

STUDIES ON THE SYNTHESIS AND
REACTIVITY OF HETEROCYCLIC
N-OXIDES

by

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Thesis presented for the degree of Doctor of Philosophy
Edinburgh University

1971



STUDIES ON THE SYNTHESIS AND
REACTIVITY OF VINYLIDENE
N-OXIDES

by

John Cameron Nelson B.Sc.

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Submitted for the degree of Doctor of Philosophy
at the University of Toronto

1971

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SUMMARY

A series of 3-aminobenzo-1,2,4-triazine derivatives has been synthesised and their oxidation with hydrogen peroxide in acetic acid studied. The position of the N-oxide group(s) in the products has been established by analysis of ^1H n.m.r. spectra. It is shown that oxidation of 3-aminobenzo-1,2,4-triazines at room temperature leads almost exclusively to the 2-oxide whereas prolonged oxidation at 50° yields the 1,4-di-N-oxide. Attempts to extend these reactions to the 3-chloro- and 3-methoxy-derivatives were unsuccessful.

A synthesis of N-hydroxy-quinoxaline N-oxides has been developed and the study of the reactions of these compounds and the analogous N-methyl-N-oxides, with acylating agents has been carried out. Acetoxylation and chlorination are respectively shown to occur exclusively at the 6-position in the fused benzene ring, on treatment with acetic anhydride and acetyl chloride. Blocking the 6-position results in substitution at the 8-position or acetoxylation of a 6-methyl group, a type of reaction not previously reported. No bromination was found to occur with acetyl bromide. The mechanisms of these substitution reactions are discussed.

Quinoxalin-3(4H)-one 1-N-oxides, with a free 2-position have been shown to undergo 1,3-dipolar cycloaddition reactions with isocyanates and benzyne to give 2-N-arylamino- and 2-(o-hydroxyphenyl)-derivatives, respectively. Reaction also occurred with phenylacetylene to give a product which appears to be dimeric but whose structure was not elucidated.

A study of the scope of the hydrogen chloride-catalysed Diels-Dilthey synthesis of oxazole N-oxides has been carried out. An alternative route to oxazole N-oxide derivatives involving the condensation of oximino carbonyl compounds with aldehydes in the presence of boron trifluoride has been developed. Oxazole N-oxides have been shown to react with phenyl isocyanate to afford products identified as 4-methyleneimidazole derivatives. Treatment of these products with acid resulted in their novel allylic rearrangement to 4-hydroxymethyl-imidazole derivatives. The course of these reactions is discussed.

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1.1. Introduction

The first heterocyclic N-oxides were prepared about 100 years ago but, in general, little interest was taken in their chemistry until about 1940.

The first synthesis of a heterocyclic N-oxide was reported by Wanklyn¹ in 1870. Up until 1929 most of the known N-oxides were recognized as being derivatives of known structures and had been previously described, e.g. pyridine N-oxide² isolated by Wanklyn in 1870 but it was not until 1924 that Prileschikoff established that this was, in fact, pyridine N-oxide (1).³

PART ONE INTRODUCTION

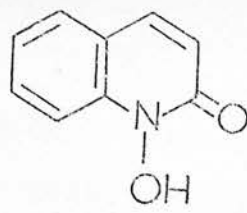
An important development in the chemistry of N-oxides was the determination by Linton⁴ in 1941 of the dipole moment of pyridine N-oxide. The unexpectedly low value (0.1 D) indicated that in addition to the structure (2), the canonical forms (3) and (4) were important contributors to the resonance hybrid. This led Schuler⁵ to predict, and later confirm, that in contrast to pyridine itself, the N-oxide should readily undergo electrophilic substitution (e.g. nitration) at the 4-position. The detailed study of the chemistry of heterocyclic N-oxides was subsequently undertaken by German workers, by Gerson⁶ who, in 1941, published a review of the chemistry of pyridine N-oxide, and by Schuler⁷ who emphasized the analogy between heterocyclic

1.1. Introduction

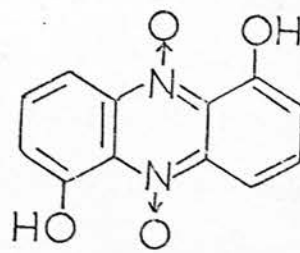
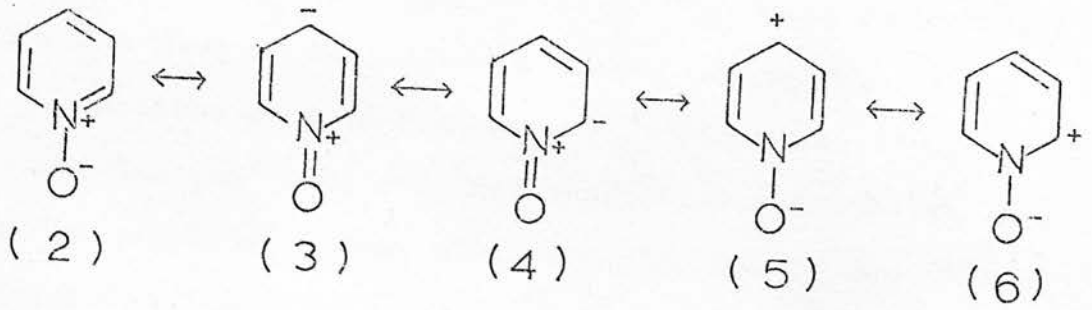
The first heterocyclic N-oxides were prepared about 100 years ago but, in general, little interest was taken in their chemistry until about 1940.

The first synthesis of a heterocyclic N-oxide was reported by Weselsky¹ in 1870. Up till 1920 most of the N-oxides synthesised were not recognised as such and many structural assignments have since had to be revised; e.g. Friedländer and Ostermaier² isolated "oxycarbostyryl" in 1881 but it was not until 1914 that Friedländer established that this compound was, in fact, carbostyryl 1-oxide (1).³ Pyridine 1-oxide was first prepared by Meisenheimer⁴ by the perbenzoic acid oxidation of pyridine and subsequent extensions of this synthetic method by Meisenheimer and Bobrański made heterocyclic N-oxides more easily obtainable.

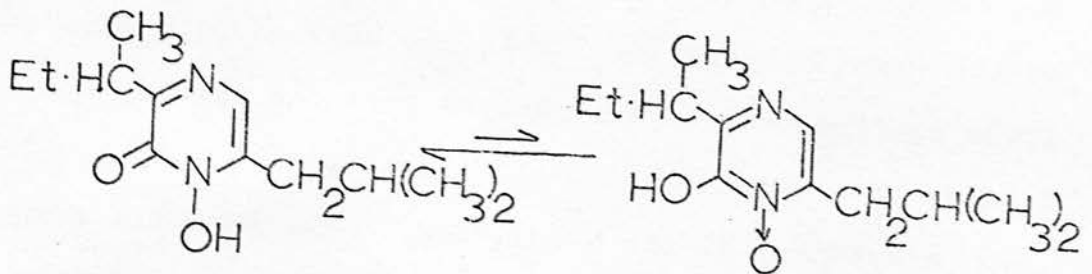
An important development in the chemistry of N-oxides was the determination by Linton⁵ in 1940 of the dipole moment of pyridine 1-oxide. The unexpectedly low value (4.24D) indicated that in addition to the structure (2), the canonical forms (3) and (4) made important contributions to the resonance hybrid. This led Ochiai⁶ to predict, and later confirm that in contrast to pyridine itself, the 1-oxide should readily undergo electrophilic substitution (e.g. nitration) at the 4-position. The detailed study of the chemistry of heterocyclic N-oxides was subsequently undertaken by Japanese workers,⁷ by den Hertog⁸ who independently discovered the nitration of pyridine 1-oxide, and by Colonna⁹ who emphasised the analogy between heterocyclic



(1)



(7)



(8)

(9)

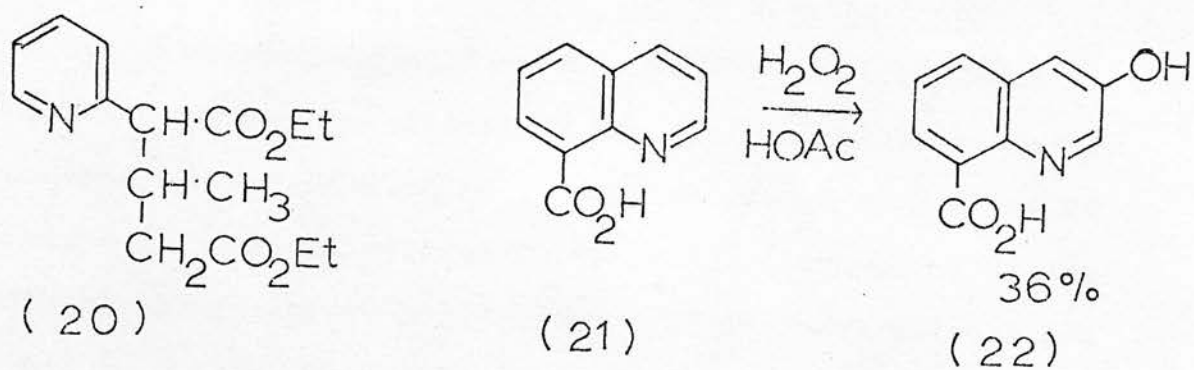
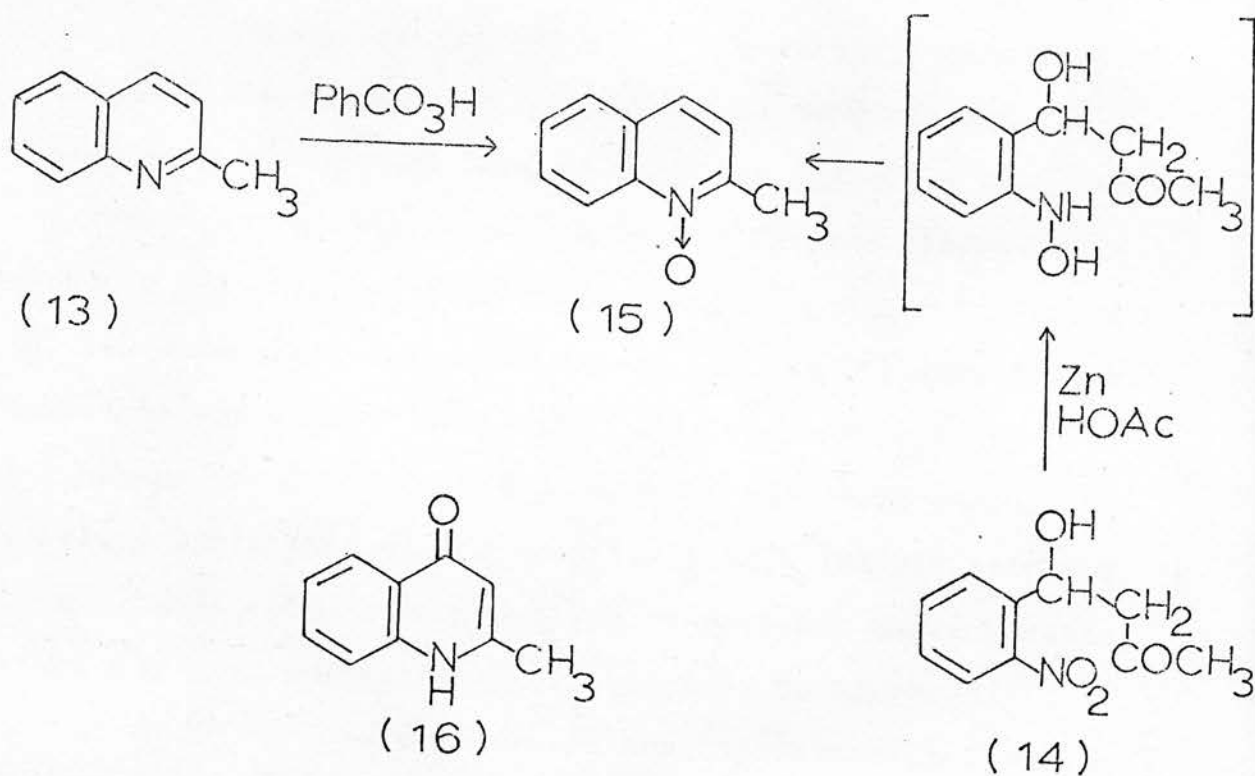
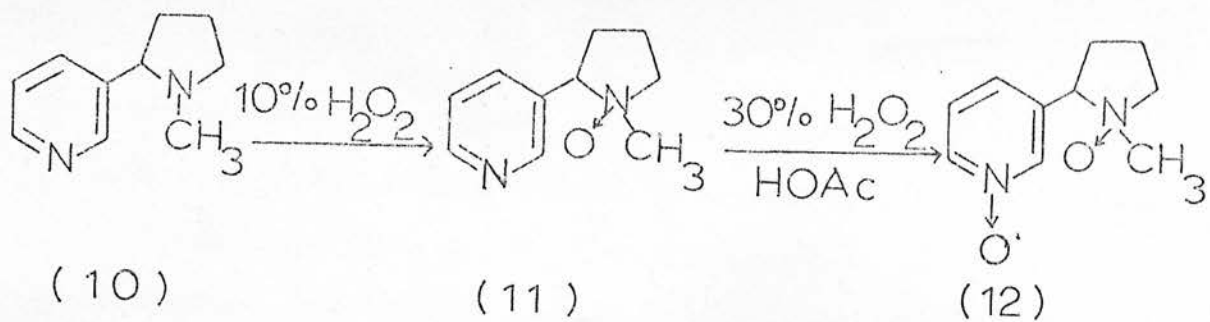
N-oxides and cyclic nitrones. It soon became apparent that the 2- and 4-positions in pyridine 1-oxide were also susceptible to nucleophilic attack, showing that the canonical forms (5) and (6) make a significant contribution to the resonance hybrid. As pointed out by Robinson,¹⁰ the ability of the N-oxide group to donate and accept electrons simultaneously rivals that of the nitroso group.

The study of the chemistry of heterocyclic N-oxides received a further stimulus in 1940 when it was discovered that certain natural products such as the antibiotics iodinin¹¹ and aspergillic acid¹² were respectively a phenazine N,N-dioxide (7) and the cyclic hydroxamic acid tautomer (8) of a pyrazine N-oxide (9). Claims^{13,14} that the conversion of certain alkaloids into their N-oxides led to reduced toxicity without a parallel decrease in biological activity added further interest to the study of N-oxide chemistry.

The field of heterocyclic N-oxides has been the subject of two text-books^{15,16} and several reviews^{7,17-21} which serve to illustrate the considerable potential for future development in this important area of heterocyclic chemistry.

1.2. The Synthesis of Heterocyclic N-Oxides.

Almost all of the known methods of preparation of heteroaromatic N-oxides may be classified as one or other of three main types, (a) Direct oxidation of the corresponding parent heterocyclic base, (b) Formation of the ring containing the N-oxide function by a cyclisation reaction, (c) Chemical modification of a cyclic N-oxide with preservation of the existing N-oxide function.



(a) Direct Oxidation

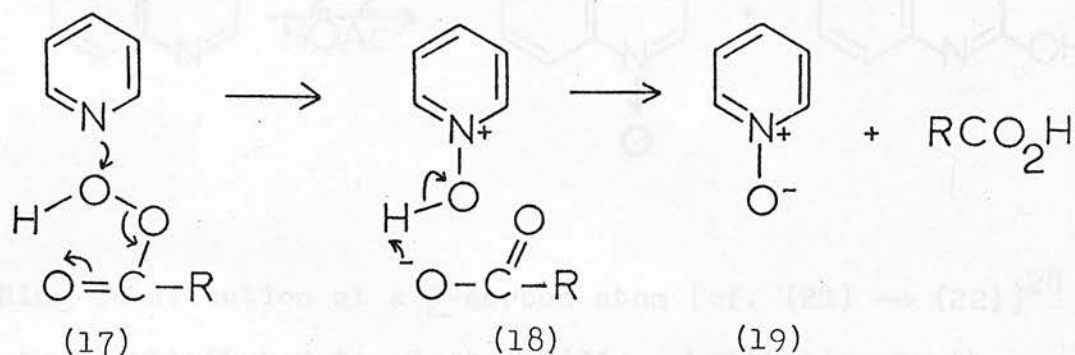
Direct oxidation of heteroaromatic compounds is the most general method of preparation for the corresponding N-oxides. Whereas aliphatic amines and sulphides are readily oxidised by hydrogen peroxide in neutral solution to the corresponding N-oxide or sulfoxide, heteroaromatic compounds are much weaker bases and require the presence of an acid to catalyse N-oxidation. Thus, oxidation of the natural product nicotine (10) with hydrogen peroxide alone gives the aliphatic mono-N-oxide (11) whereas the di-N-oxide (12) is obtained on treatment with peracetic acid.²²

In 1925, Meisenheimer and Stotz²³ found that reaction of quinaldine (13) with perbenzoic acid afforded a product identical to that obtained by reduction of 4-hydroxy-4-(o-nitrophenyl)-butan-2-one (14) with zinc in acetic acid.²⁴ They showed that the oxidation product was quinaldine 1-oxide (15) and not the quinolone (16). Soon afterwards Meisenheimer showed that perbenzoic acid would oxidise other heterocyclic bases to their N-oxides and since then a number of percarboxylic acids, in particular monopero-phthalic, m-chloroperbenzoic and peracetic acids have been developed for this purpose. The most convenient and widely used of these reagents is peracetic acid which is normally prepared in situ from glacial acetic acid and 30% aqueous hydrogen peroxide. The reaction conditions usually involve heating at a temperature between 20° and 90° for 3-24 h. Pertrifluoroacetic acid has been used for the oxidation of hindered compounds such as 2,6-dibromopyridine which

resists oxidation by perbenzoic and peracetic acids.

Inorganic acids such as sulphuric or phosphoric acid have been utilised as catalysts but the yields are very low.

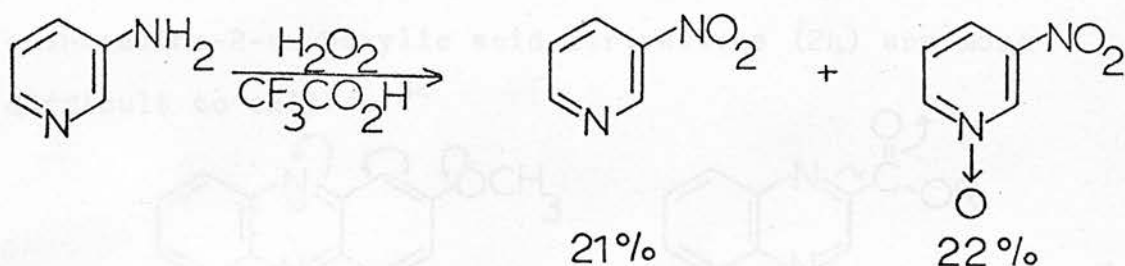
The mechanism of peracid oxidation is well understood and involves nucleophilic attack by the ring nitrogen atom at the oxygen atom of the hydroxyl group in the peracid as shown [(17) \rightarrow (19)] -



The ease of oxidation depends mainly on the basicity of the nitrogen atom and the electron-withdrawing power of the acyl moiety of the peracid.

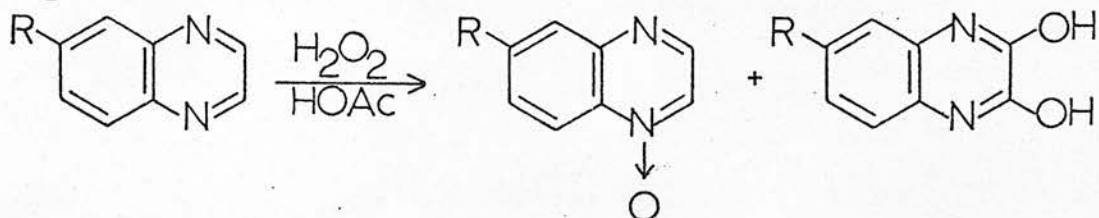
Despite its widespread use in the synthesis of N-oxides, peracid oxidation is sometimes complicated by side reactions, usually of an oxidative nature. This is especially marked in the case of peracetic acid where reaction conditions involve heating for a long period of time. A further complication is hydrolysis in the acidic medium.

A primary amino group is sometimes oxidised to a nitro group²⁵ -



Likewise the formation of N-oxides is sometimes accompanied by oxidative degradation, picolinic acid N-oxide being obtained²⁶ by oxidation of compound (20).

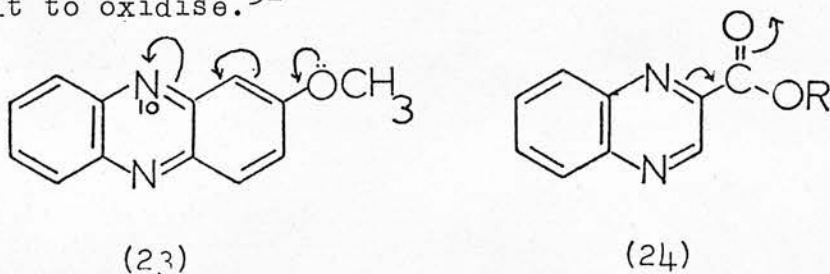
By acting as a nucleophile the peracid can form α - or γ -hydroxy heterocycles as well as N-oxides.
e.g.²⁷

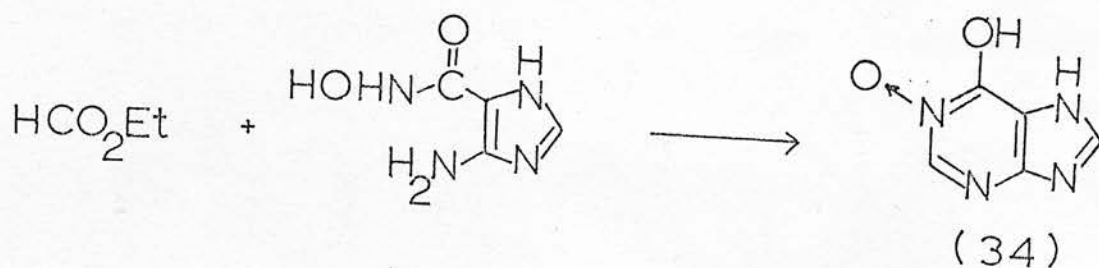
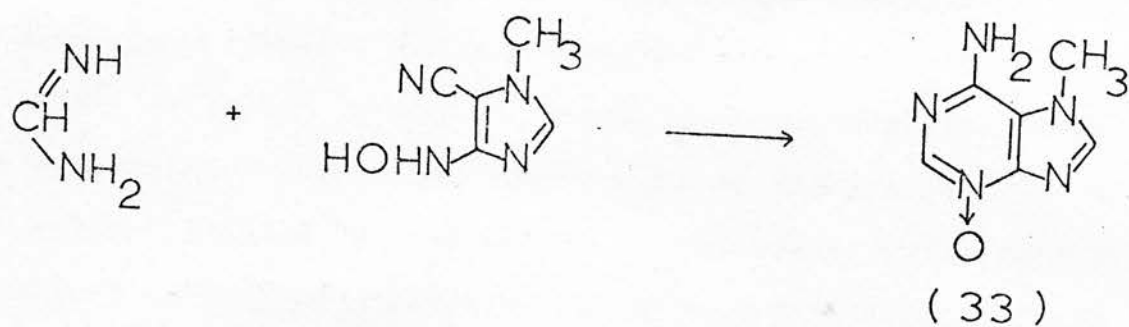
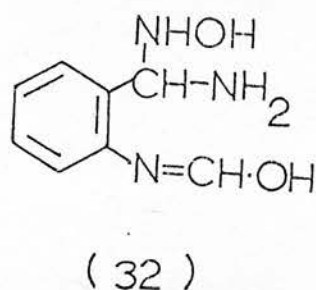
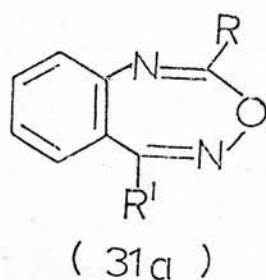
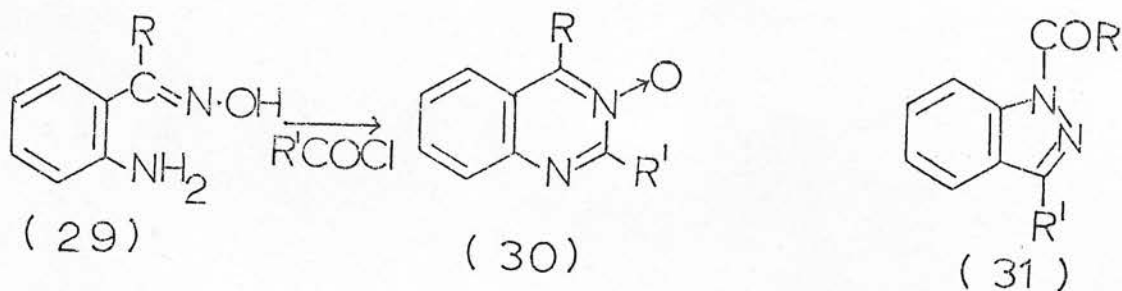
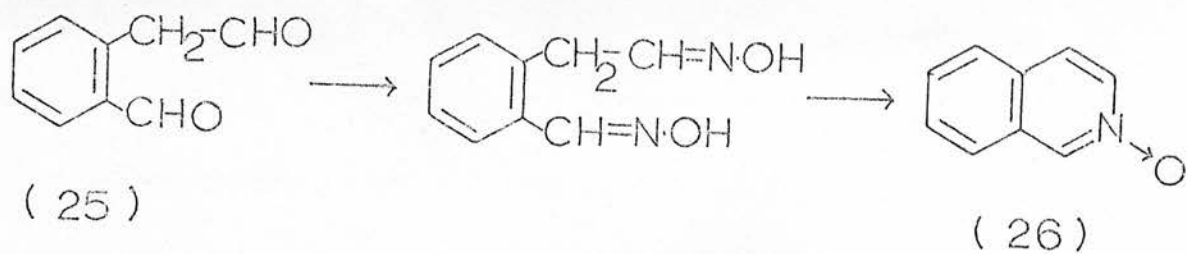


Ring substitution at a β -carbon atom [cf. (21) \rightarrow (22)]²⁸ may be attributed to electrophilic substitution by the peracid.

N-Oxidation by peracids is subject to steric hindrance. Peracid oxidation of 2,6-diphenylpyridine affords the N-oxide only in low yield.²⁹ Likewise while 2,3-dimethylquinoxaline can be oxidised to the di-N-oxide, its 2-methyl-3-isopropyl analogue only forms a mono-N-oxide and 2,3-diisopropylquinoxaline is stable to oxidation.³⁰

Substituents in the nucleus affect the ease of N-oxidation by increasing or decreasing the availability of the lone electron pair on the nitrogen atom. Thus 2-methoxyphenazine (23) affords predominantly the 10-oxide³¹ but quinoxaline-2-carboxylic acid derivatives (24) are more difficult to oxidise.³²



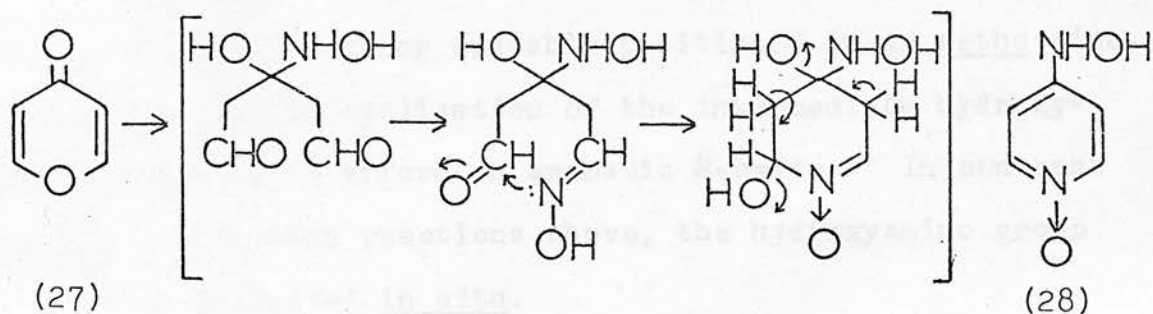


(b) Cyclisation Reactions

Cyclisation reactions leading to heterocyclic N-oxides are of several distinct types -

(i) Cyclisation of Hydroxylamine Derivatives

Baumgarten³³ showed that substituted glutaconic dialdehydes undergo ring-formation when treated with hydroxylamine to afford pyridine 1-oxides. Analogously homophthalaldehyde (25) yields isoquinoline 2-oxide (26).³⁴ γ -Pyrone (27) may be regarded as the dienol anhydride of a 1,5-dicarbonyl compound and on treatment with hydroxylamine forms 4-hydroxyaminopyridine 1-oxide (28),³⁵ presumably by cyclisation of an oxime intermediate.



If a substituent that reacts with the hydroxyamino or oxime group is present in the γ or δ position, cyclisation to form an N-oxide is possible. Thus o-aminobenzaldoximes (29) react with acid anhydrides (or chlorides) to afford quinazoline 3-oxides (30).³⁶ The products of these reactions had previously been described as acylindazoles (31)³⁷ and benzoxadiazepines (31a).³⁸ Confusion no doubt arose because syn-aldoximes give benzoxadiazepines whereas the anti-aldoximes form isomeric quinazoline 3-oxides.³⁹ Adachi⁴⁰ found that treatment of quinazolines with hydroxylamine afforded the

corresponding quinazoline 3-oxides, probably via the intermediate (32). These methods are useful for the synthesis of quinazoline 3-oxides since peracid oxidation of quinazoline and 4-alkoxyquinazolines yields respectively 4-quinazolinol⁴⁰ and 4-alkoxyquinazoline 1-oxides.⁴¹

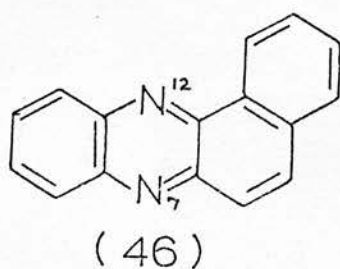
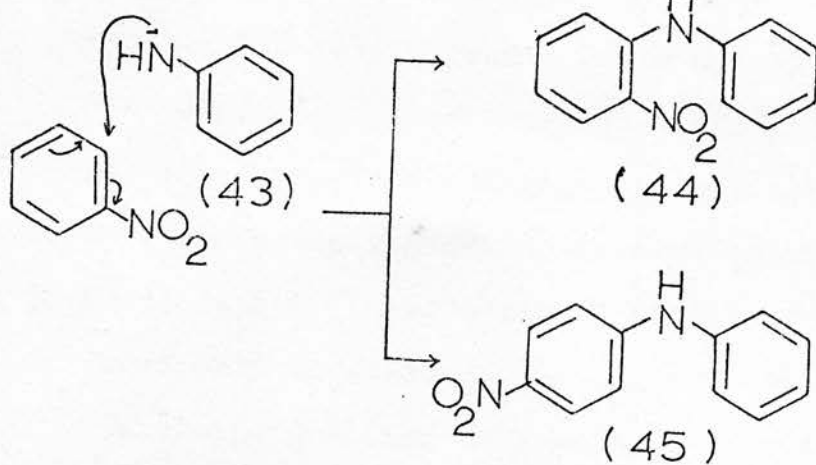
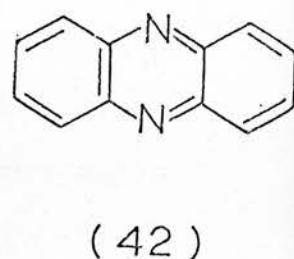
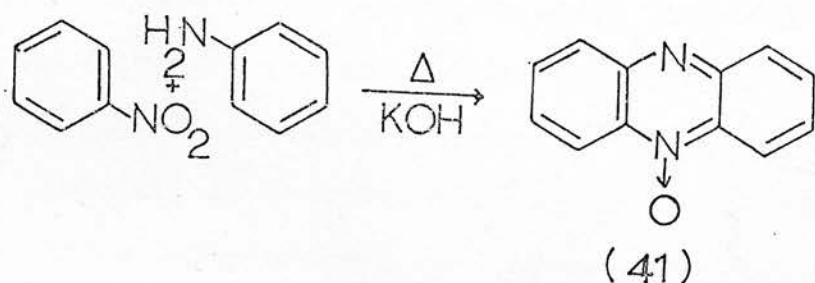
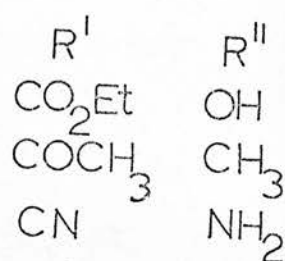
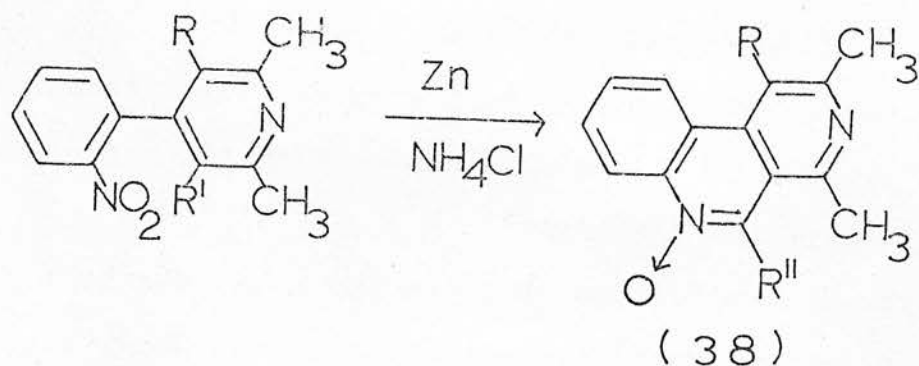
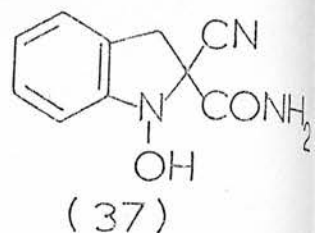
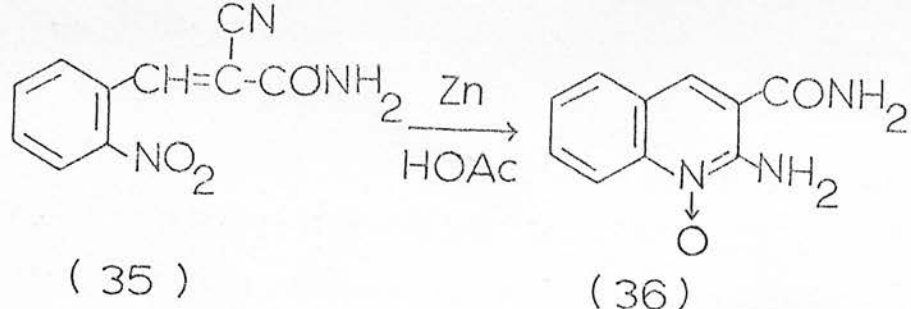
The monoximes of α,β -dicarbonyl compounds are themselves incapable of cyclisation but will condense with aminonitriles to form 2-aminopyrazine N-oxides.⁴²

This type of cyclisation reaction has been used to prepare mono-N-oxides of polyazaheterocyclic compounds, e.g. the purine-3-oxide (33)⁴³ and the purine 1-oxide (34).⁴⁴

(ii) Reductive Cyclisation of Nitro Compounds

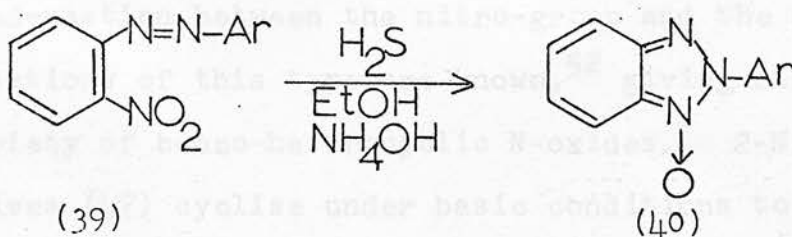
Reduction of aromatic nitro compounds which possess a carbonyl or amino group suitably positioned in an ortho-side-chain, results in cyclisation of the intermediate hydroxy-amino compound to afford an aromatic N-oxide. In contrast to the cyclisation reactions above, the hydroxyamino group has to be generated in situ.

The classic example of this type of N-oxide synthesis is the cyclisation of the nitro compound (14) to quinaldine 1-oxide (15).²³ Similarly the product of reductive cyclisation of o-nitrobenzylidenecyanoacetamide (35) was shown by Taylor⁴⁵ to be 2-amino-3-carbamoylquinoline 1-oxide (36) and not the dihydroindole derivative (37) postulated by Heller.⁴⁶ Many quinoline 1-oxide derivatives have been synthesised by this method using such reducing agents as ammonium sulphide, hydrazine, palladium-charcoal/sodium borohydride, and hydrogen in the presence of palladium-



kieselguhr. This method can be extended to nitro compounds in which the reactive group is contained in an adjacent ring as in the synthesis of compounds such as 2,9-diazaphenanthrene 9-oxides (38).⁴⁷

However, N-oxides of the quinoline series can be readily prepared by direct oxidation and this method of reductive cyclisation has been developed more for the synthesis of benzazole N-oxides for which it is indispensable. This type of synthesis can be exemplified by the mild reduction of *o*-nitroazobenzene derivatives (39) to benzotriazole 1-oxides (40).⁴⁸

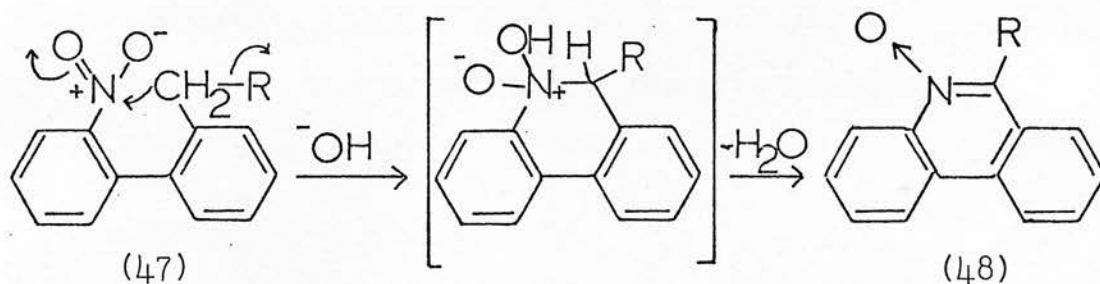


(iii) Intermolecular and Intramolecular Condensation Reactions of Nitro Compounds

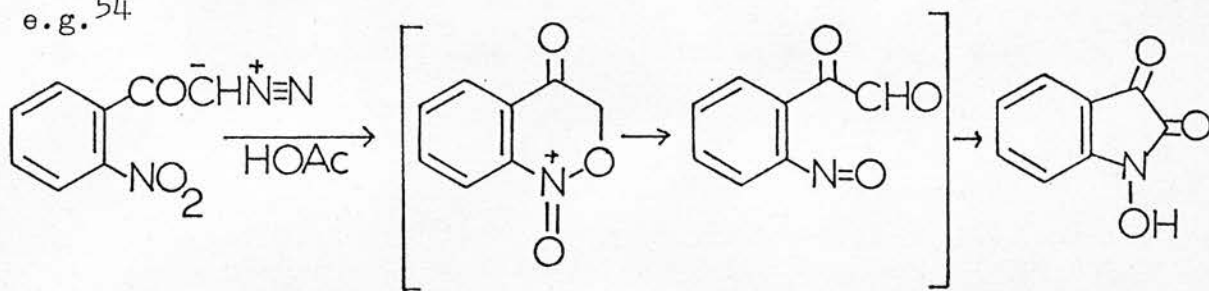
The reaction of arylamines and aromatic nitro compounds in the presence of strong alkali at 110-160°, the Wohl-Aue reaction,⁴⁹ results in the formation of phenazine 5-oxide (41) and phenazine (42) in poor yields. The mechanism is thought to involve initial nucleophilic attack by the aromatic amino anion (43) on the nitro compound, followed by reductive cyclisation of the resulting *o*-nitrodiarylamine (44). This hypothesis is based on the observed formation of *p*-nitrodiphenylamine (45) as by-product.⁵⁰ Despite the poor yield and concurrent formation of phenazine, the Wohl-Aue reaction

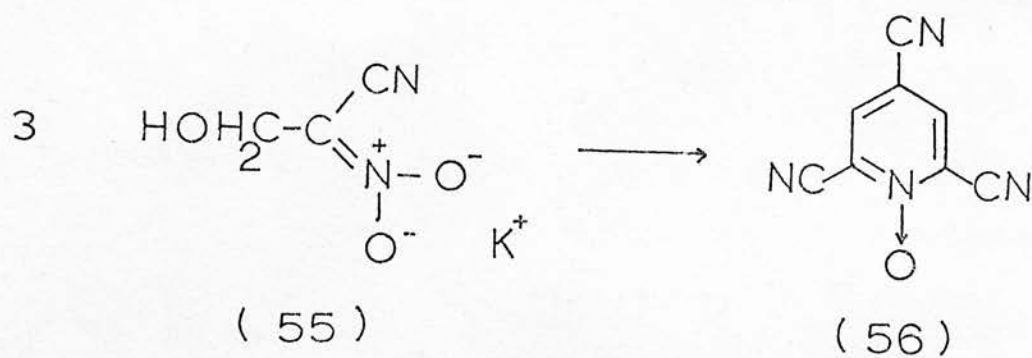
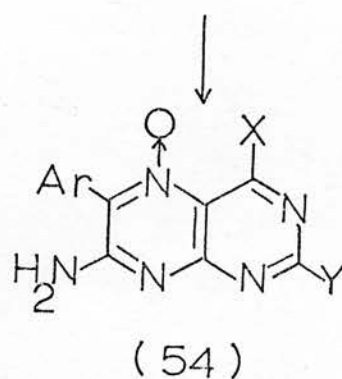
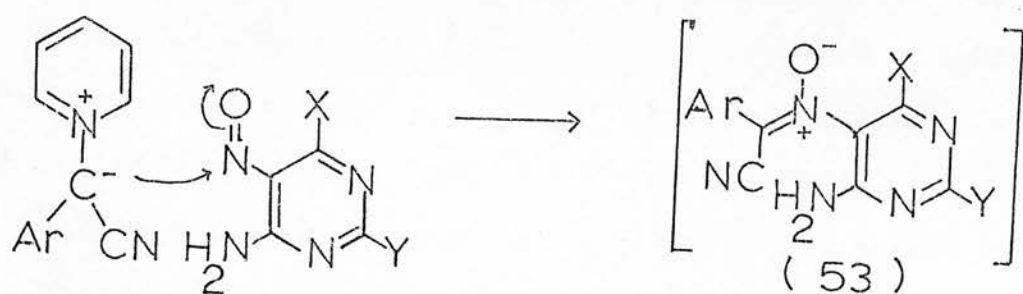
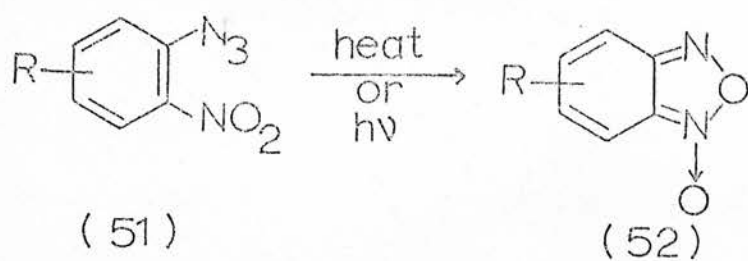
has been used to synthesise N-oxides of systems such as benzo-[a]-phenazine (46). Direct oxidation of compound (46) yields only the 7-oxide because of steric hindrance, but the 12-oxide can be synthesised by the Wohl-Aue reaction from nitrobenzene and β -naphthylamine.⁵¹

In some cases an aromatic nitro-group can undergo condensation in the presence of acid or alkali, with an active methylene-group in an ortho-side-chain. The available evidence indicates that, although mechanisms involving nitroso or hydroxylamino intermediates cannot be ruled out, the most likely mechanism involves direct aldol-type condensation between the nitro-group and the side-chain. Many reactions of this type are known,⁵² giving rise to a wide variety of benzo-heterocyclic N-oxides. 2-Nitrobiphenyl derivatives (47) cyclise under basic conditions to yield derivatives of phenanthridine 5-oxide (48),⁵³ but only if the group R is electron-withdrawing (e.g., cyano, carbamoyl, methoxycarbonyl).

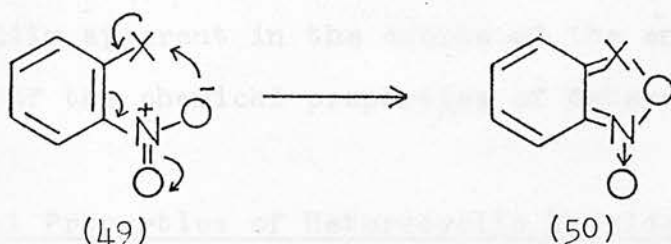


Cyclisation reactions of nitrobenzene derivatives also occur under acidic conditions - e.g.⁵⁴





Ring closure reactions of nitro compounds can also occur in which both oxygen atoms are retained in the heterocyclic ring. In such reactions ring closure is of the type (49) \rightarrow (50).



This normally gives rise to 5-membered heterocyclic N-oxides. A good example of this type is the preparation of benzo-1,2,5-oxadiazole 2-oxides (benzofuroxans) (52)⁵⁵ which can be obtained by pyrolysis or photolysis of *o*-nitrophenyl azides (51).

(iv) Cyclisation of Nitron derivatives

On the basis of the idea that aromatic N-oxides can be regarded as cyclic nitrones,⁹ syntheses have been devised involving the cyclisation of an intermediate nitron (derived from a nitroso compound). An example of this type of reaction is the formation of the pteridine 5-oxide (54)⁵⁶ from the nitron (53).

(v) Miscellaneous cyclisations

There are a variety of N-oxide preparations which do not appear to fit into any of the above categories. For instance, 2,4,6-tricyano-pyridine 1-oxide (56)⁵⁷ has been prepared from salts of the cyanonitrolic acid (55) but details of the reaction mechanism are obscure.

(c) Chemical Modification of Cyclic N-Oxides

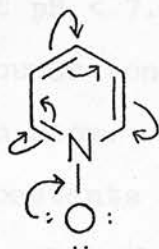
Heteroaromatic N-oxides prepared by chemical modification of existing cyclic N-oxides are too numerous to be discussed at this stage. However, examples will become readily apparent in the course of the ensuing discussion of the chemical properties of heterocyclic N-oxides.

1.3. Physical Properties of Heterocyclic N-Oxides

Whereas the four atomic orbitals of the nitrogen atom in an aliphatic N-oxide are approximately tetrahedral (sp^3) in structure, the lone pair of electrons on the nitrogen atom in a heterocyclic base are contained in an sp^2 orbital. Thus in an aromatic N-oxide the nitrogen-oxygen bond is in the same plane as the hetero-ring, and the $2p\pi$ -atomic orbital of its oxygen atom is in a plane parallel to the orbitals of the hetero-ring atoms. The resulting large-interaction between the nitrogen-oxygen bond and the π -electron system of the ring constitutes the main reason for the characteristic behaviour of aromatic N-oxides [c.f. resonance structures (2)–(6)] and explains the difference in reactivity compared with either the corresponding heterocyclic base or aliphatic N-oxides.

As previously mentioned, the low value for the dipole moment of pyridine 1-oxide⁵ is due to conjugation of the negatively charged oxygen atom with the aromatic ring, the shift of electrons from the oxygen atom to the ring opposing the dipole moment of the N-oxide group.

i.e.



The conjugation is even higher in condensed heteroaromatic systems and as a result the polarity of the N-oxide group is lowered. A comparison of the dipole moments of a number of γ -substituted pyridines and their N-oxides⁵⁸ showed that in addition to the above-mentioned conjugation there is also a shift of electrons in the opposite direction [c.f. resonance structures (5) and (6)].

X-ray crystallographic analysis of 4-nitropyridine 1-oxide⁵⁹ shows that the nitrogen-oxygen bond lengths are different in the nitro (1.189Å) and N-oxide (1.260Å) groups. This is consistent with the observed absorptions in the infrared spectrum, attributable to the N^+-O^- stretching vibrations of the nitro and N-oxide groups. All aromatic N-oxides exhibit intense absorptions in the region of 1300-1200 cm^{-1} .

Half-wave reduction potentials of the nitrogen-oxygen bond in representative unsubstituted heterocyclic N-oxides indicate that reduction occurs at a far more negative potential than for aliphatic N-oxides. This resistance to reduction indicates the greater stability of the nitrogen-oxygen bond in heteroaromatic N-oxides. The reduction potential of the nitrogen-oxygen bond varies with pH,

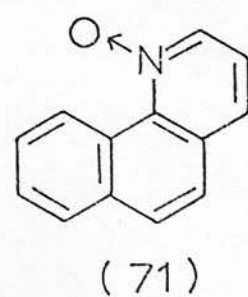
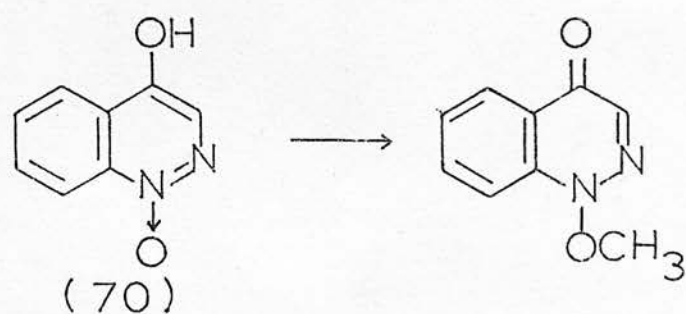
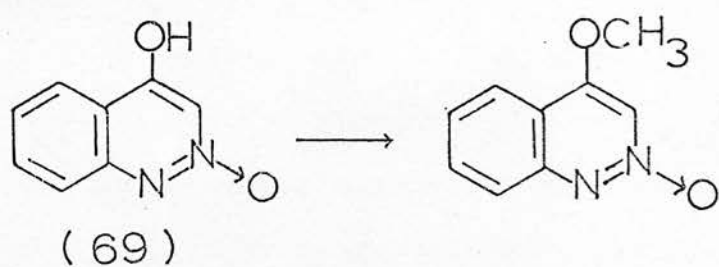
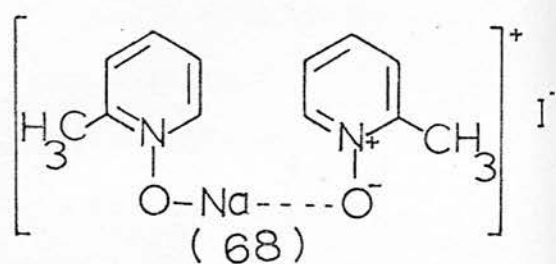
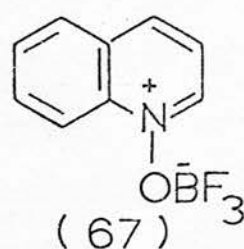
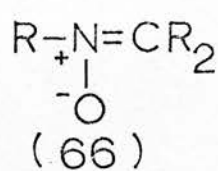
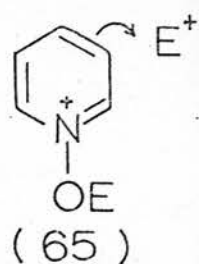
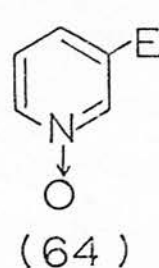
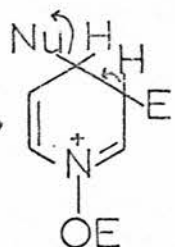
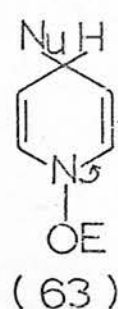
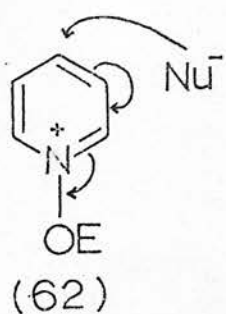
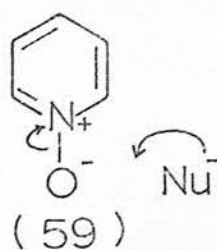
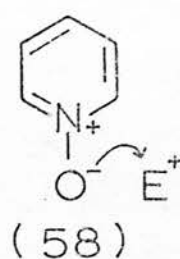
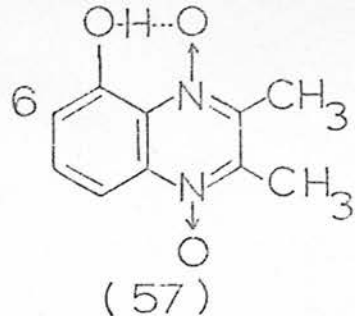
reduction being easier at $\text{pH} < 7$. Polarographic reduction is also easier with compounds containing a fused benzene ring or a second nitrogen atom.

The dissociation constants (pK_a) of the conjugate acids of aromatic N-oxides vary, but the values are lower than those of the parent bases and much lower than those of aliphatic N-oxides. Thus the conjugative effect implicit in the structures (2) and (3) must exist considerably in aqueous solution, and the decreased negativity of oxygen may account for the small pK_a values observed.

Nuclear magnetic resonance (NMR) studies on the effect of N-oxidation on the chemical shift of protons in the parent base have demonstrated the dual electron-donating and electron-withdrawing properties of the N-oxide group. Also, protons in a peri-position to an N-oxide group experience a magnetic anisotropy effect.

Mass spectral studies⁶⁰ indicate that an intense (M-16) peak is characteristic of aromatic N-oxides and that many N-oxides also show strong (M-17) peaks.

The N-oxide group shows a tendency to form an intramolecular hydrogen bond. This has been shown for 2,3-dimethyl-5-hydroxyquinoxaline 1,4-dioxide (57) by the relative solubilities in organic solvents of (57) and its 6-hydroxy isomer.⁶¹ Hydrogen bonding, which hinders reduction in some cases, can also be detected spectroscopically or by chelation with copper.



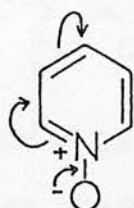
1.4. Chemical Properties of Heterocyclic N-Oxides

(a) General Survey

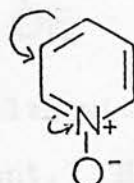
Because of the ability of the N-oxide group to exert both an electron-releasing and an electron-withdrawing effect simultaneously (see before for pyridine 1-oxide), N-oxides show great variety in their chemical reactions.

Attack at the oxygen atom by electrophiles (E) as in (58), and by nucleophiles (Nu) as in (59), can take place.

Both electrophiles and nucleophiles can attack at carbon atoms α - and γ - to the N-oxide group because electron displacements of types (60) and (61) are possible.



(60)



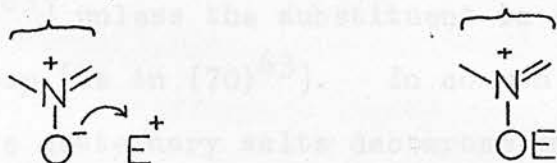
(61)

Electrophilic substitution at the α -carbon atom is, however, rarely observed, being opposed by the strong adverse inductive effect of the neighbouring positively charged nitrogen atom. Many reactions involving attack by weak nucleophiles (e.g. acetic anhydride) require the preliminary reaction of an electrophile at the oxygen atom, as in (62). Other reactions appear to involve the rearrangement of such a coordinated intermediate giving rise to substitution at the α -carbon atom possibly via a cyclic transition state. Substitution has also been found to occur at a position β or δ to the N-oxide group and this could be explained by the sequences (63) \rightarrow (64) or (65) \rightarrow (64).

In reactions with nucleophiles heterocyclic N-oxides sometimes behave similarly to nitrones (66)⁹ and like nitrones can also undergo 1,3-dipolar cycloaddition reactions involving cyclic transition states.

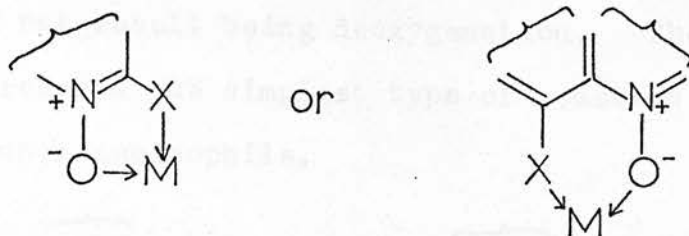
(b) Electrophilic Attack at the Oxygen Atom

The oxygen atom in the aromatic N-oxide group is basic and will undergo addition with a variety of electrophiles (e.g. acids, alkyl halides, Lewis acids), to give adducts which may be stable or react further, depending on the reagent employed.



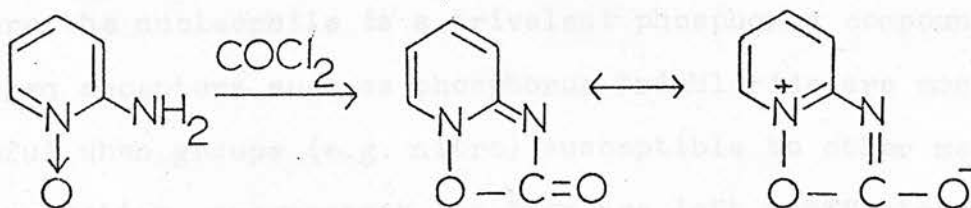
Aromatic N-oxides form stable salts with strong acids unless another negative group is present. However, the basicity of N-oxides is considerably less than that of the parent base and varies with the substituent in the aromatic ring. The basicities of a number of substituted N-oxides have been shown to fit the Hammett equation with $\rho = 2.09$.⁶² The salts formed with acids (e.g. picrates, hydrochlorides) are usually crystalline and are used in the purification and characterisation of aromatic N-oxides.

The oxygen atom of the N-oxide group can also combine with Lewis acids, such as boron trifluoride, to form complexes such as (67). Addition to metal ions can form complexes of the type (68) by a process similar to the hydrogen bonding described above. If a suitable substituent is situated *ortho*- or *peri* to the N-oxide function even more stable chelated derivatives are formed -



Aromatic N-oxides react with alkylating agents such as alkyl halides and alkyl sulphonates, particularly in polar solvents (e.g. acetonitrile), yielding O-alkyl derivatives in the form of quaternary salts. However, if the molecule contains a substituent which will alkylate under these conditions, substituent alkylation occurs preferentially [as in (69)⁶³] unless the substituent is conjugated with the N-oxide group [as in (70)⁶³]. In common with the aliphatic series these quaternary salts decompose on heating with alkali, to yield the tertiary amine and an aldehyde.

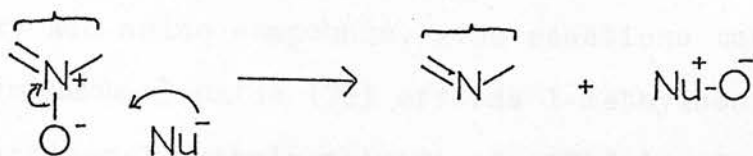
The adducts formed between aromatic N-oxides and acyl halides are generally even more reactive than the O-alkyl derivatives above, and are consequently very difficult to isolate. However, in some situations, as shown below,⁶⁴ the acylating agent can react with the oxygen atom of the N-oxide group to form an intramolecular acyl derivative.



(c) Nucleophilic Attack at the Oxygen Atom

Reducing agents and some other electron donors such as phosphorus trichloride supply an electron pair to the oxygen

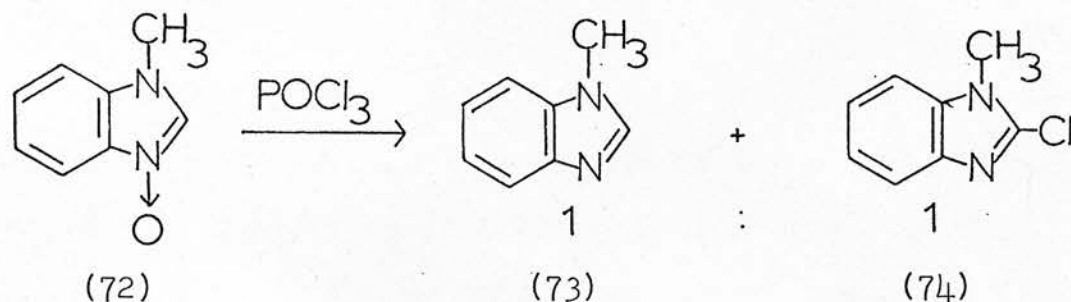
atom, the net result being deoxygenation. The sequence below represents the simplest type of reaction between an N-oxide and a nucleophile.



Aromatic N-oxides are generally much more resistant to deoxygenation than aliphatic N-oxides. Whereas treatment with sulphurous acid at room temperature will reduce an aliphatic N-oxide to the corresponding tertiary amine, in general, aromatic N-oxides are resistant to this type of reduction. This difference in the ease of reduction has been used to selectively reduce the aliphatic N-oxide group in nicotine N,N'-dioxide (12).⁶⁵ However, the sulphurous acid reduction of the benzo-[h]-quinoline N-oxide (71)⁶⁶ is an exception. Measurement of polarographic reduction potentials has shown that the presence of condensed rings and/or a greater number of nitrogen atoms in the molecule greatly increases the ease of reduction of aromatic N-oxides.

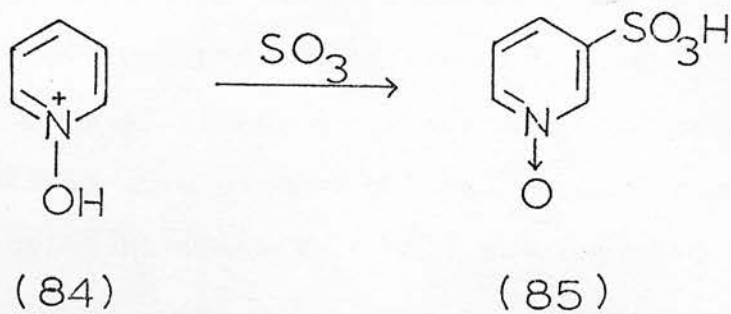
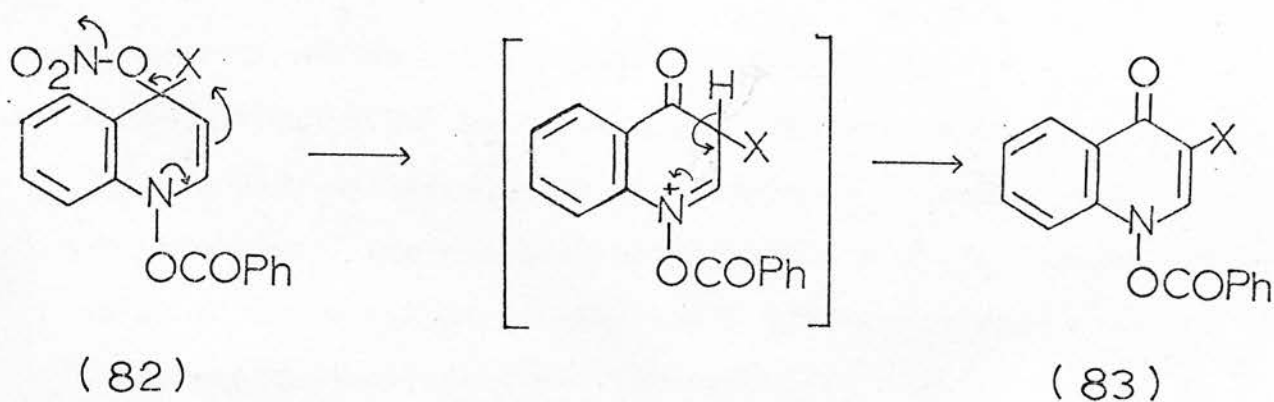
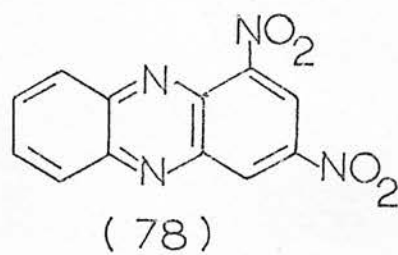
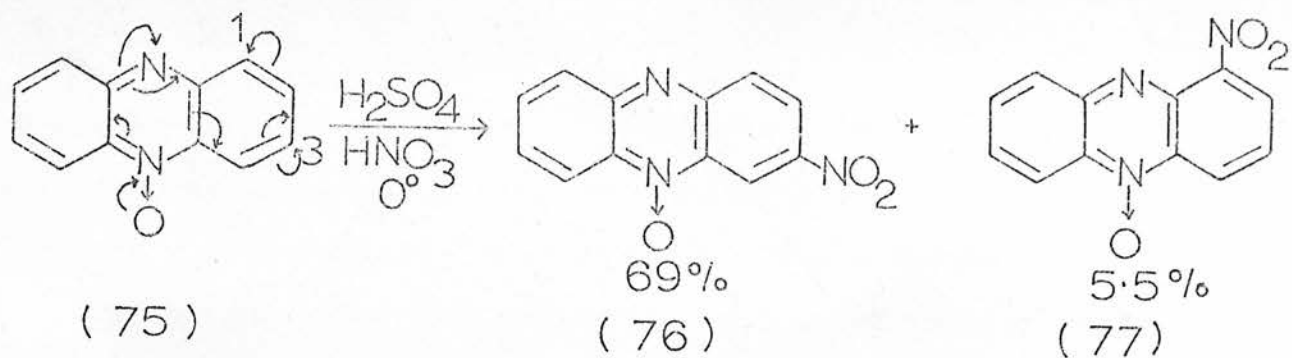
Probably the best known reaction of this type occurs where the nucleophile is a trivalent phosphorus compound. Oxygen acceptors such as phosphorus trichloride are most useful when groups (e.g. nitro) susceptible to other methods of reduction, are present, as they are left unaffected. Other trivalent phosphorus compounds can also be used but require more vigorous reaction conditions than phosphorus trichloride. The mechanism of these reactions, although

simply represented above, is in some cases more complex and can involve radical-chain reactions. Although the reaction with phosphorus trichloride proceeds in good yield, except with hydroxy and amino compounds, side reactions can occur. Thus 1-methylbenzimidazole 3-oxide (72) affords 1-methylbenzimidazole (73) and 2-chloro-1-methylbenzimidazole (74) in almost equal quantities.⁶⁷



Catalytic hydrogenation, usually at the surface of a solid-phase catalyst, has been widely used for the reduction of N-oxides. Hydrogenation over palladium-charcoal or Raney nickel, at atmospheric pressure and temperature has been most frequently used. Raney nickel tends to be more selective than palladium for the reduction of N-oxides containing other reducible groups.

Deoxygenation can also be achieved successfully by reduction with iron or zinc in acetic acid, a variety of compounds of sulphur (e.g. sodium dithionite), and complex metal hydrides. In some cases, heating alone or in acid solution in the presence of an oxidising agent, also results in deoxygenation. Thus on heating with acetic acid and hydrogen peroxide the 7,12-di-N-oxide of benzo-[a]-phenazine (46) is reduced to the 7-mono-N-oxide,⁵¹ reoxidation being prevented by steric hindrance.

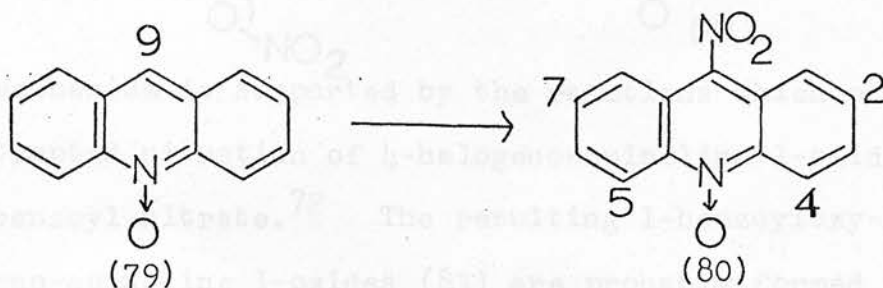


(d) Electrophilic Substitution

Heterocyclic compounds containing nitrogen are reluctant to undergo electrophilic substitution because of the electron attracting properties of the nitrogen atom. Where substitution does take place it occurs at the β -position which has a higher electron density than either the α - or the γ -position. Conversion of a heterocyclic base to its N-oxide causes changes in electronic structure which promotes attack at the α - and γ -positions [c.f. resonance structures (2)-(4)]. Substitution at the γ -position should proceed especially readily since the conjugative effect at the α -position is partly offset by the adverse inductive effect due to the adjacent nitrogen atom. These predictions, which are backed up by quantum-mechanical calculations suggest that electrophilic substitution in the N-oxide ought to occur more readily than for the parent base. These contentions have been firmly established particularly in the case of pyridine and quinoline 1-oxides.

The study of the electrophilic substitution reactions of aromatic N-oxides dates from the discovery by Ochiai,⁶ and later independently by den Hertog,⁸ that heating of pyridine 1-oxide with potassium nitrate in fuming sulphuric acid at 100° affords 4-nitropyridine 1-oxide in high yield. Nitration of phenazine affords 1,3-dinitrophenazine (78) only at 60°, whereas nitration of phenazine 5-oxide (75) occurs readily at 0° giving mainly 3-nitrophenazine 5-oxide (76) and a small amount of 1-nitrophenazine 5-oxide (77).⁶⁸ In this case the polar effect of the N-oxide is transmitted into

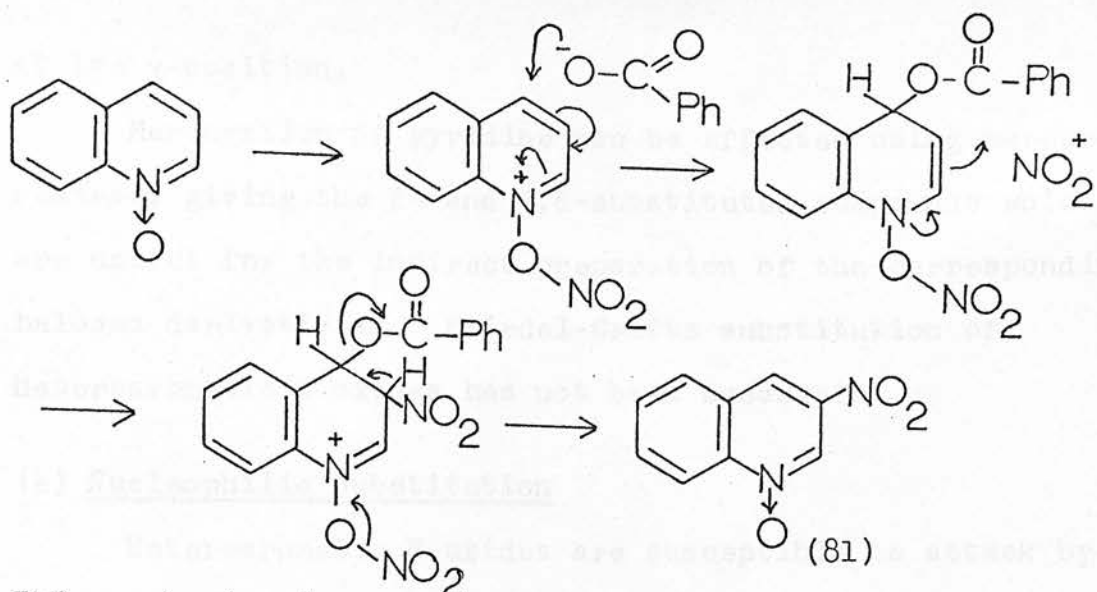
the adjacent fused benzene ring. The polar effect of the N-oxide group directs nitration into the 4-position in pyridazines and cinnolines. It is particularly marked in the case of acridine 10-oxide (79) which yields 9-nitro-acridine 10-oxide (80)⁶⁹ whereas electrophilic substitution in acridine itself, occurs first at the 2- and 7-positions and then at the 4- and 5-positions.



The course of the nitration of quinoline 1-oxide is dependent on temperature and the acidity of the reaction medium. Between 0° and 10° substitution occurs at the 5- and 8-positions as in quinoline, but above 40° the N-oxide group directs substitution into the 4-position.⁷

The orienting effect of the N-oxide group is very great compared with most substituents in the ring. Thus 2-ethoxy- and 3-ethoxy-pyridine 1-oxide both nitrate exclusively in the 4-position.⁷⁰ Steric effects can however prevent nitration at the activated γ -position.

Substitution β - to the N-oxide group has been observed by Ochiai and Kaneko⁷¹ using acyl nitrates. Benzoyl nitrate converts quinoline 1-oxide into 3-nitroquinoline 1-oxide (81) by the mechanism shown.



This mechanism is supported by the reactions which occur on attempted nitration of 4-halogeno-quinoline 1-oxides with benzoyl nitrate.⁷² The resulting 1-benzoyloxy-3-halogeno-quinoline 1-oxides (83) are probably formed from the intermediate (82).

In contrast to nitration, other types of electrophilic substitution in heteroaromatic N-oxides do not proceed so readily. 4-Bromoquinoline 1-oxide⁷ and 9-bromoacridine 10-oxide⁶⁹ are obtained by the direct bromination of the corresponding N-oxides. However, bromination of pyridine 1-oxides requires very harsh conditions and affords very poor yields. Various 3-bromo derivatives have been obtained⁷³ by a reaction analogous to the β -nitration of N-oxides described above.

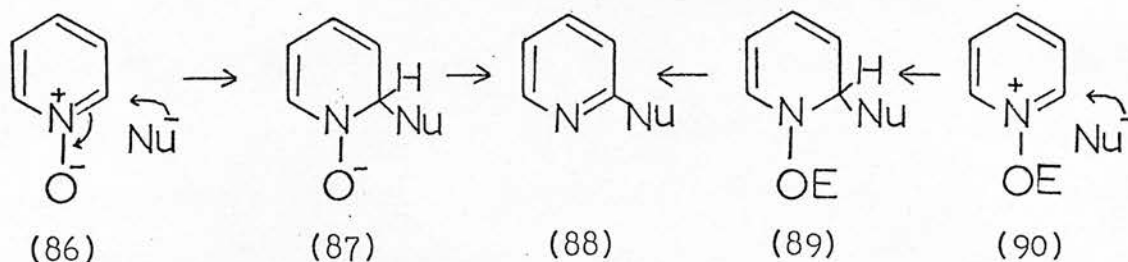
Sulphonation likewise occurs much less readily than nitration and for pyridine 1-oxide only takes place at 230° using oleum in the presence of a mercuric sulphate catalyst.⁷⁴ The 3-sulphonic acid (85) obtained is almost certainly the result of sulphonation of the N-oxide conjugate acid (84). Electrophilic attack on the free base would have occurred

at the γ -position.

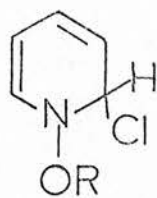
Mercuration of pyridine can be effected using mercurous acetate, giving the 2- and 2,6-substituted compounds which are useful for the indirect preparation of the corresponding halogen derivatives. Friedel-Crafts substitution of heteroaromatic N-oxides has not been successful.

(e) Nucleophilic Substitution

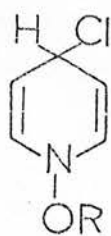
Heteroaromatic N-oxides are susceptible to attack by nucleophilic reagents by virtue of the electron-withdrawing effect of the N-oxide group [c.f. canonical forms (5) and (6)]. Strong nucleophiles (e.g. Grignard reagents) are capable of attacking an unactivated N-oxide at the α -carbon atom [(86) \rightarrow (87) \rightarrow (88)], but weaker nucleophiles (e.g. chloride ion) can usually only attack the α - or γ -carbon atom if the N-oxide first coordinates with an electrophile [(90) \rightarrow (89) \rightarrow (88)]. Nucleophilic substitution occurs primarily at the α -position where the mesomeric and inductive effects are superposed and in nearly all cases subsequent deoxygenation gives the substituted heterocycle (88).



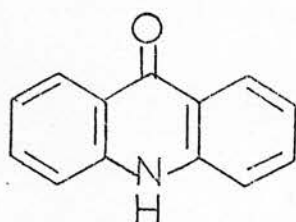
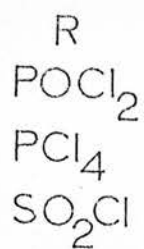
Grignard reagents and organolithium compounds react with heterocyclic N-oxides to give α -alkyl and α -aryl heterocycles. Thus quinoline 1-oxide reacts with phenylmagnesium bromide to yield 2-phenylquinoline.⁷⁵ The yields



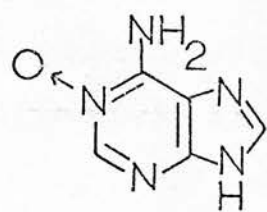
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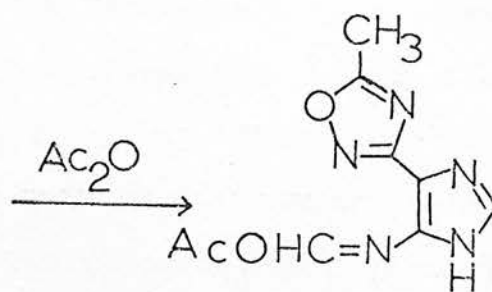
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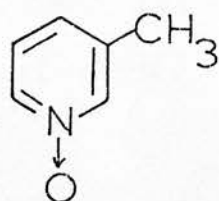
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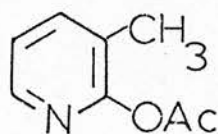
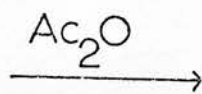
(94)



(95)



(96)



(97)

in the reaction of heterocyclic N-oxides with organometallic compounds are not good but can be improved by carrying out the substitution using the corresponding N-alkoxy quaternary salts [(90); E = alkyl].

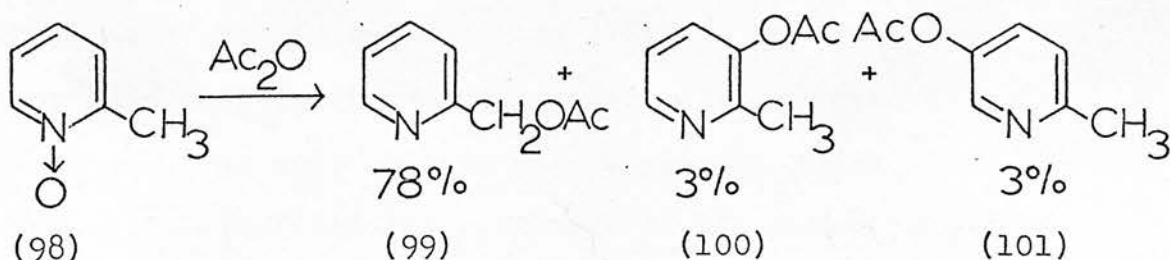
Although the direct chlorination of heterocyclic N-oxides does not yield satisfactory results, α - and γ -chloro-heterocycles are formed by the action of phosphorus oxychloride, phosphorus pentachloride or sulphuryl chloride (SO_2Cl_2). In contrast to the reaction with organometallic compounds, 2-chloro- and 4-chloro-pyridine are formed in almost equal amounts,⁷⁶ presumably via the intermediates (91) and (92). Although reaction with these reagents gives rise predominantly to α - and γ -substitution, examples are known of displacement of groups (e.g. nitro) by chloro, or substitution in a side-chain, in a fused benzenoid ring, or β - to the N-oxide group.

One of the most general reactions of heteroaromatic N-oxides is their conversion by Reissert-type reactions into α -cyano derivatives. For example, quinoline 1-oxide reacts with benzoyl chloride and potassium cyanide to afford 2-cyanoquinoline⁷⁷ probably by way of the intermediate (89; E = C(Ph), Nu = CN). If a free α - position is not available, substitution sometimes takes place at the γ -position. Thus acridine 10-oxide gives 9-cyanoacridine.⁷⁸

Katada⁷⁹ was the first to report that reaction of pyridine 1-oxide with acetic anhydride gave rise to 2-acetoxypyridine (103). This reaction has been considerably developed for other heterocyclic systems and is widely used in the

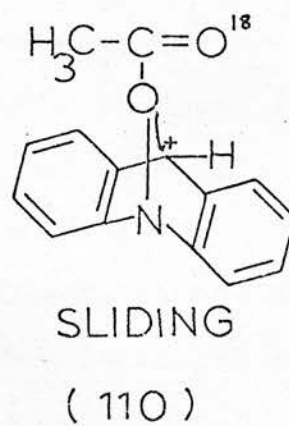
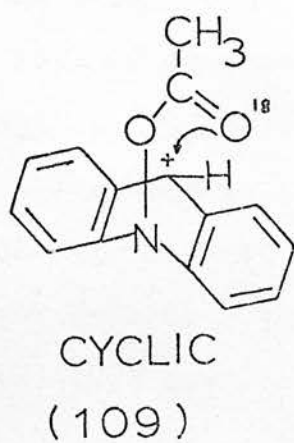
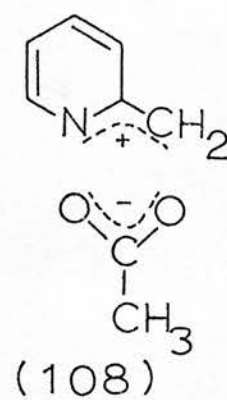
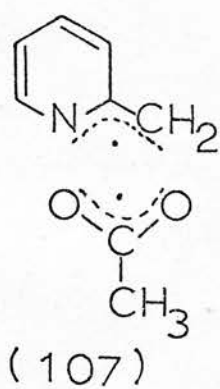
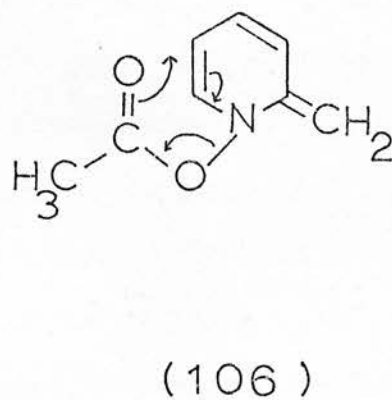
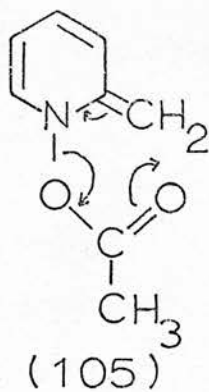
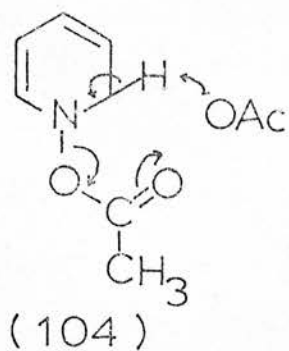
synthesis of alcohols and the derived carbonyl compounds because of the easy hydrolysis of the α -acetoxy derivatives initially obtained. Although there is a very strong tendency for substitution to occur at the α -position, if both α -positions are occupied reaction can occur at the γ -position. Thus acridine 10-oxide yields 9-acridone (93).⁸⁰ Adenine 1-oxide (94), however, in its reaction with acetic anhydride undergoes cleavage of the pyrimidine ring to give the imidazalyl-oxadiazole derivative (95).⁸¹

Treatment of 3-picoline 1-oxide (96) with acetic anhydride affords the α -acetoxy pyridine (97);⁸² but when α - or γ -alkyl N-oxides are treated with acetic anhydride, side-chain acetoxylation occurs. Thus 2-picoline 1-oxide (98) affords the acetoxymethyl derivative (99) as the major product, and the β -acetoxy derivatives (100) and (101) as by-products.^{82,83}

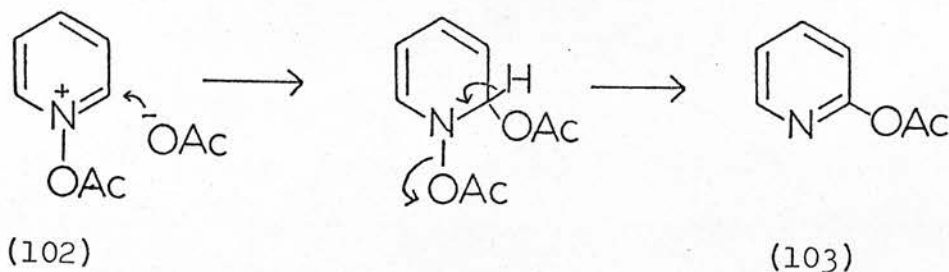


Mechanistic investigations of these reactions have shown that, although a general pathway can be written for the reaction of heterocyclic N-oxides with acid anhydrides, no single mechanism seems to fit all of the facts.

The mechanism of the reaction between pyridine 1-oxide and acetic anhydride appears to involve initial formation of the N-acetoxypyridinium ion (102) followed by rate-determining

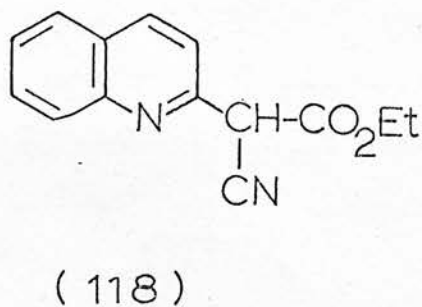
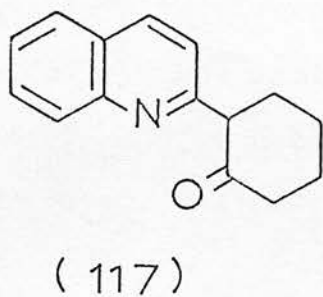
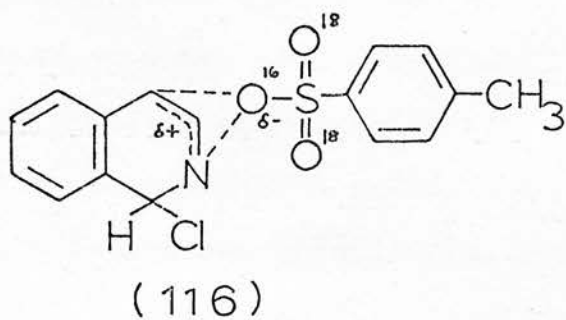
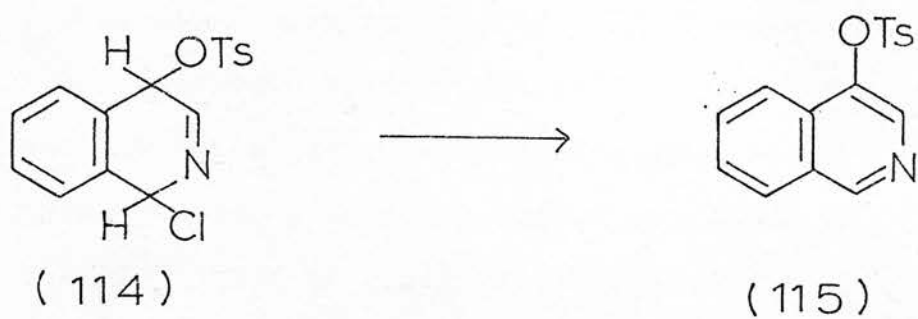
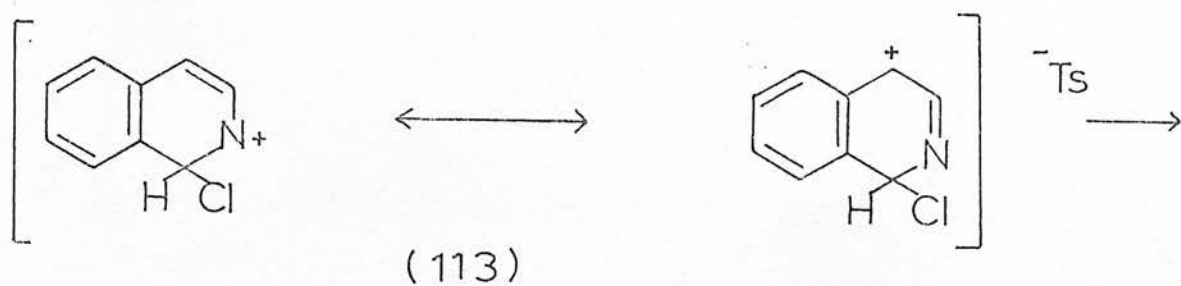


intermolecular nucleophilic addition of acetate ion
[c.f. (102)→(103)].



This is consistent with the pseudo first-order kinetics⁸⁴ and the results of ^{18}O -labelling experiments,⁸⁵ which rule out the possibility of an intramolecular process (104).

The mechanism of the reaction between 2-picoline 1-oxide and acetic anhydride (and of the related conversion of 4-picoline 1-oxide into 4-acetoxymethylpyridine) has been the subject of much controversy. It is generally accepted that an intermediate, similar to (102) is formed, followed by base-catalysed abstraction of a proton from the methyl group to yield the anhydro base (105). Japanese investigators^{83,86} originally proposed a mechanism involving ionisation and anionotropic rearrangement, but Bullitt and Maynard⁸⁷ postulated rearrangement of the anhydro base as shown [(105) and (106)], and Boekelheide and Harrington⁸⁸ suggested a radical-chain process. Later workers,⁸⁹ although finding evidence for radical intermediates showed that the reaction rate was unaffected by radical inhibitors and thus could not proceed predominantly by a radical-chain mechanism. Decisive evidence against the cyclic rearrangement of the anhydro base was provided by the ^{18}O -labelling studies of Oae⁹⁰ which showed that the two oxygen atoms



became equivalent in the course of reaction. Oae suggested that a solvent-caged radical pair (107) was involved, but the most recent evidence⁹¹⁻⁹³ comes out strongly in favour of ion-pair intermediates (108). Similarly the presence of 4-picolyl cations rather than 4-picolyl radicals has been observed⁹⁴ although this reaction appears to be both intra- and intermolecular.

¹⁸O-tracer experiments appear to indicate that the reaction of acridine 10-oxide with acetic anhydride is very complex, involving two distinct intramolecular paths (109) and (110).⁸⁰

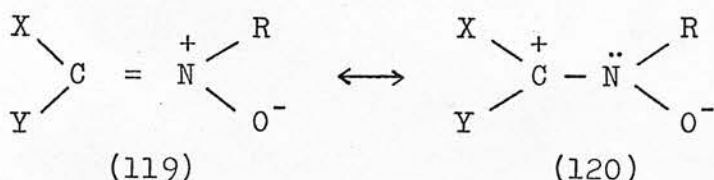
The reaction of heterocyclic N-oxides with tosyl chloride in an aqueous alkaline medium gives rise to α -oxo heterocycles (e.g. quinoline 1-oxide \rightarrow carbostyryl) through nucleophilic substitution by hydroxide ions. Treatment of heterocyclic N-oxides with tosyl chloride alone, shows many similarities to the reactions with acetic anhydride. Thus 2-picoline 1-oxides yield 2-chloromethyl derivatives and β -tosyloxy heterocycles can also be obtained. None of the mechanisms already proposed can accommodate the formation of 4-tosyloxyisoquinoline (115)⁹⁵ from isoquinoline 2-oxide (111) and tosylchloride. Ochiai⁹⁵ suggested that the intermediates (112)-(114) were involved in the reaction but more recent ¹⁸O-tracer studies⁹⁶ suggest that (116) represents the major pathway in this rearrangement.

Heterocyclic N-oxides have been reacted with a variety of other nucleophiles after prior formation of the N-alkoxy-quaternary salt (62), giving rise to α - and γ -substituted

heterocycles. Thus quinoline 1-oxide reacts with the enamine of cyclohexanone and benzoyl chloride to yield 2-(2-quinolyl) cyclohexanone (117);⁹⁷ and with ethyl cyanoacetate and acetic anhydride to afford (118).⁹⁸ Mercaptans (e.g. butanethiol) have been used as nucleophiles to form thio derivatives.

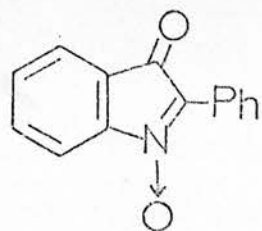
(f) 1,3-Dipolar Cycloaddition

A heterocyclic N-oxide can be regarded as a type of cyclic nitron because of the similar mesomerism (119) \longleftrightarrow (120) possible for nitrones.

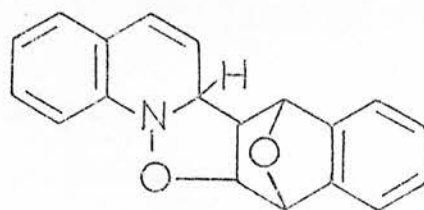


Although heteroaromatic N-oxides (e.g. quinoline 1-oxide) are not always so strikingly similar because of considerable delocalisation of the positive charge, an N-oxide such as 2-phenylisatogen (121) is a good example of a cyclic nitron. Consequently, as with nitrones, 1,3-dipolar cycloaddition reactions can occur.⁹⁹ During formation of the adduct the aromaticity of the N-oxide ring is lost. The strong driving force to regain this aromaticity causes further transformation of the adduct, so that the apparent overall result is nucleophilic substitution and deoxygenation.

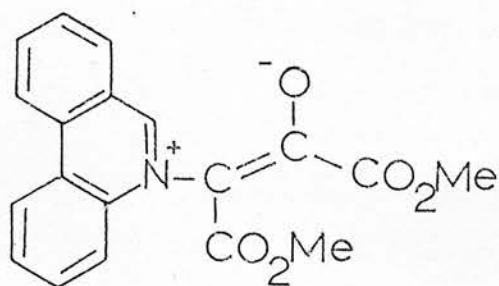
The reaction with phenyl isocyanate is typical, giving adducts of the type (122) which break down spontaneously to yield anilino derivatives (123).⁹⁹



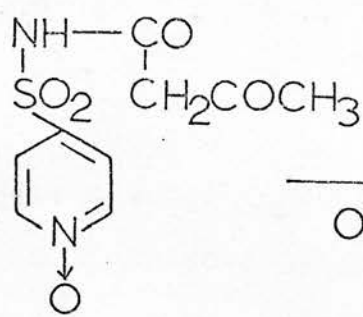
(121)



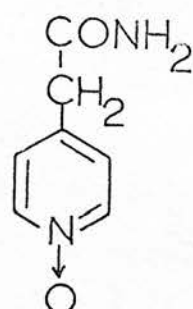
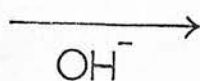
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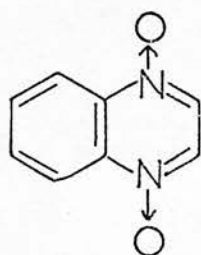
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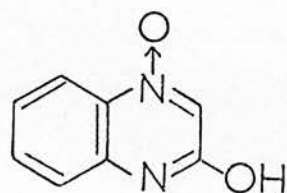
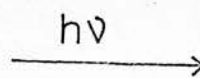
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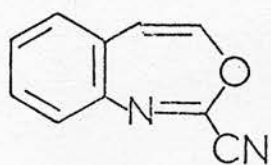
(129)



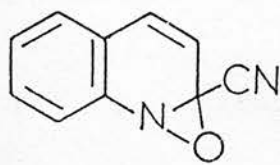
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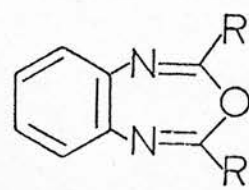
(131)



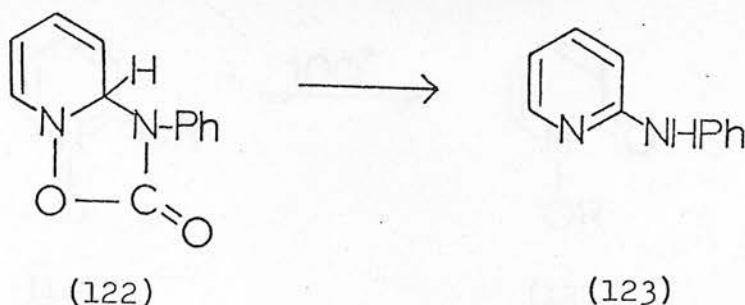
(135)



(136)



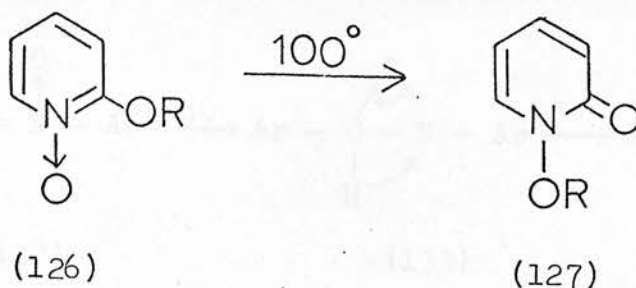
(137)



Cycloadditions of this type have been reported for many ring systems. Although the intermediate adducts are generally very labile, some have been isolated [e.g. (124)¹⁰⁰]. In some cases the adduct can rearrange to give zwitterionic products. This behaviour is exemplified by the formation of (125) by the reaction of phenanthridine 5-oxide with dimethyl acetylene dicarboxylate.¹⁰¹ Cycloaddition reactions of benzimidazole N-oxides with dipolarophiles such as carbon disulphide, methyl propiolate, benzonitrile and benzyne have been thoroughly investigated by Kano and Takahashi.¹⁰²

(g) Rearrangements

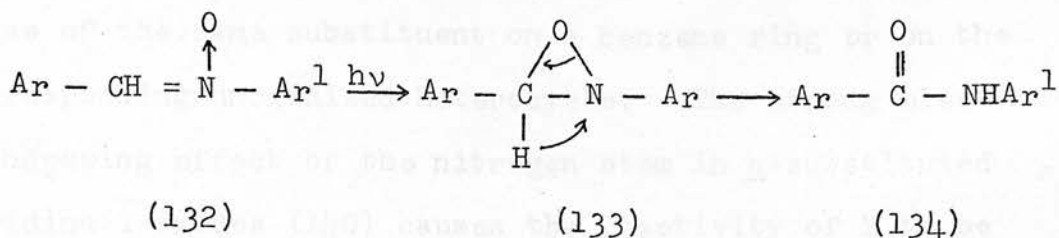
As already discussed, heterocyclic N-oxides react with acid anhydrides and acid chlorides giving products apparently formed by transfer of the nitrogen-bound oxygen to the α -position on the ring or to an α -side-chain. The generally accepted mechanism involves acylation of the N-oxide oxygen atom, inferring that the reaction is triggered by the nucleophilic activity of the oxygen atom. Examples are known of true molecular rearrangements of this type in which no external reagent is involved. Thus 2-alkoxypyridine 1-oxides (126) rearrange on heating at a comparatively low temperature to give the corresponding N-alkoxy-2-pyridone (127) in good yield.¹⁰³



The similar rearrangement of 2-methoxypyridine is known to be promoted by the presence of benzoyl peroxide but in the corresponding N-oxide rearrangement there is no evidence for a radical mechanism, and an ionic process has been proposed.

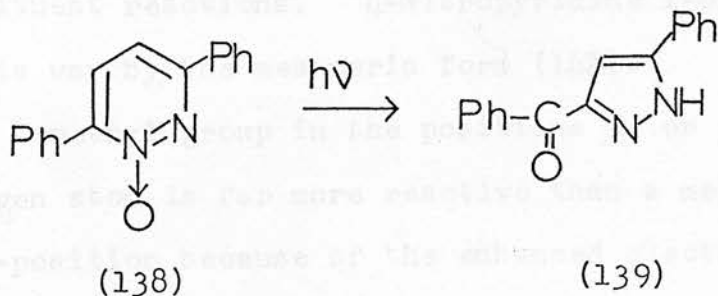
A base-catalysed rearrangement involving nucleophilic addition to the α - or γ -position in the ring is exemplified by the conversion of N-acetoacetyl-4-pyridine sulphonamide 1-oxide (128) and related compounds into products of the type (129).¹⁰⁴

Recently a considerable amount of work has been carried out on the study of photochemical rearrangements of heterocyclic N-oxides, notably by research groups in Japan, France and Denmark. These studies have revealed a fascinating variety of rearrangements involving N-oxides. Irradiation of quinoxaline 1,4-dioxide (130) with ultra-violet light or sunlight yields 2-hydroxyquinoxaline 4-oxide (131).^{105,106} Photochemical rearrangements of this type involving transfer of the oxygen atom to a position α - to the nitrogen atom have also been observed with nitrones. It has been proved that the nitrone (132) is isomerised photochemically to the oxaziridine (133), and that this unstable system decomposes to the acid amide (134).¹⁰⁷



It is assumed that the photochemical rearrangements of heterocyclic N-oxides also proceed via similar oxaziridine intermediates. Attempts have been made to isolate these oxaziridines but in nearly all cases it has become clear that the first isolable products are usually oxazepines. Thus the first product isolated from the irradiation of 2-cyanoquinoline 1-oxide is the oxazepine (135)¹⁰⁸ and not the oxaziridine (136), as previously postulated.¹⁰⁹ Similarly, the unstable primary photo-product of various substituted quinoxaline mono-N-oxides have been shown to be symmetrical oxadiazepines (137).¹¹⁰

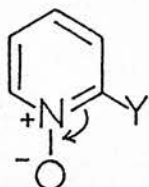
As an example of ring contraction by photochemical irradiation, the pyridazine 1-oxide (138) affords the pyrazole derivative (139).¹¹¹



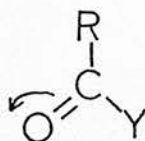
(h) Influence of the N-Oxide Group on the Reactivity of Substituents

Substituents in the α - or γ -position to an N-oxide group display chemical properties which are different from

those of the same substituent on a benzene ring or on the corresponding unoxidised heterocycle. The strong electron-withdrawing effect of the nitrogen atom in α -substituted pyridine 1-oxides (140) causes the reactivity of Y to be similar to that in the structure (141). This effect is enhanced in quaternary derivatives of N-oxides.



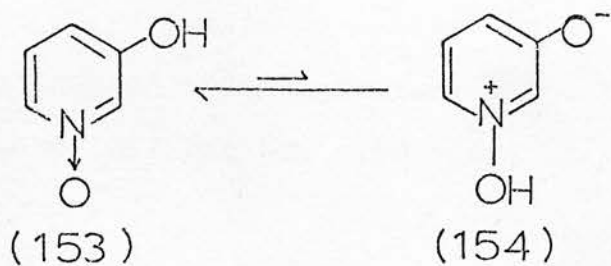
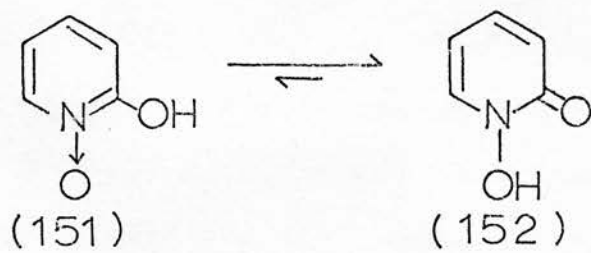
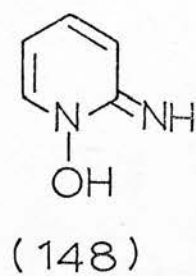
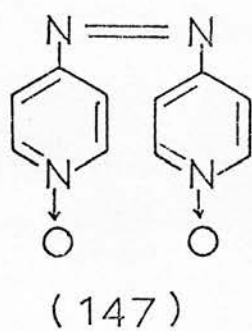
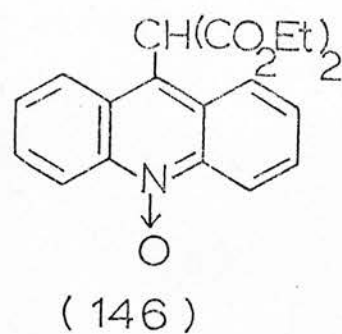
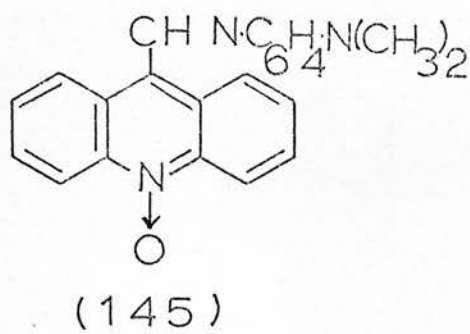
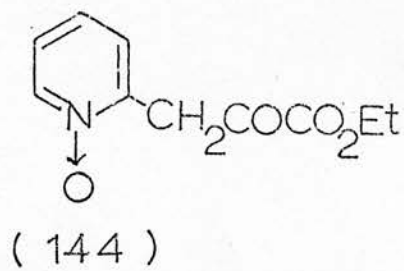
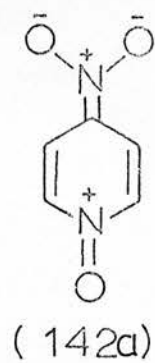
(140)



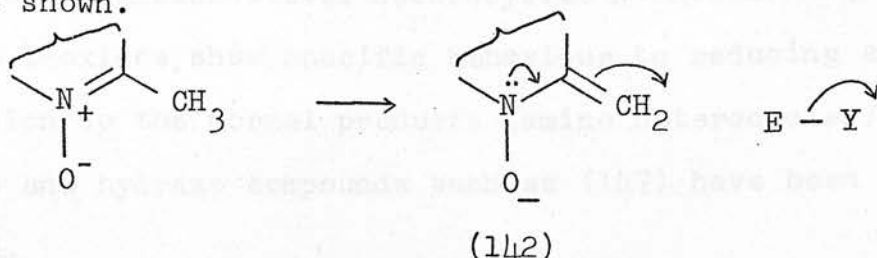
(141)

It follows that some substituents (e.g. chloro, nitro) will more readily undergo nucleophilic displacement; the acidity of the α' -hydrogen atom on a substituent is enhanced (thus tautomerism can occur); and α -carboxyl or carboxymethyl groups will decarboxylate readily. These effects may be transmitted through a vinyl group. In addition, the electron-donating ability of the N-oxide group is important in some substituent reactions. 4-Nitropyridine 1-oxide is stabilised in this way by the mesomeric form (142a).

A methyl group in the positions α - or γ - to the ring nitrogen atom is far more reactive than a methyl group in the β -position because of the enhanced electron-withdrawing effect of the N-oxide group. It has been shown that this activating effect is increased by N-oxidation, although not as much as by quaternisation of either the parent heterocycle or the N-oxide. The rearrangement reactions of picoline 1-oxides with acid anhydrides and acid chlorides have already



been discussed. Reactions in which the N-oxide group is retained involve initial proton loss to form a mesomeric anion of the type (142) which then reacts with an electrophile as shown.



The increased mobility of a methyl group hydrogen atom in N-oxides compared with the parent heterocycles is shown by the reaction of 2-picoline 1-oxide with diethyl oxalate to give (144),¹¹² the product of Claisen condensation. Many α - and γ -methyl heterocyclic N-oxides will also react with aromatic aldehydes under basic conditions to form ethylene derivatives, and react with aromatic nitroso compounds to form anils. Thus (145) is obtained from 9-methylacridine 10-oxide and N,N-dimethyl-p-nitrosoaniline.¹¹³

The ability of the N-oxide group to lower the electron density at the α - and γ - positions on the ring increases the mobility of halogen substituents at these positions, compared with the parent heterocycles. Halogen atoms at these positions are often easily displaced by nucleophiles such as alkoxides, amines, thiols and active methylene compounds. 9-Chloroacridine 10-oxide reacts with diethyl sodiomalonate in this manner, to yield (146).¹¹³

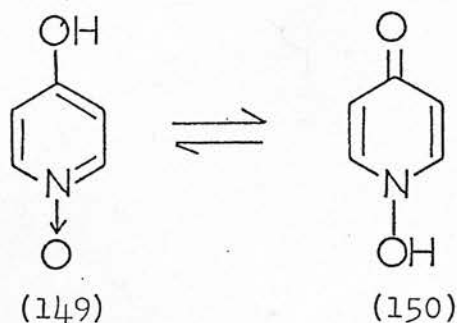
Nitro groups at the α - or γ -positions to an N-oxide group are also activated towards nucleophilic displacement which occurs readily with most nucleophiles. However,

efforts to replace the nitro-group in 3-nitropyridine 1-oxide have failed. As the nitro-group is readily introduced into the 4-position, its replacement is an important method for preparing 4-substituted heterocyclic N-oxides. 4-nitropyridine 1-oxides show specific behaviour to reducing agents. In addition to the normal products (amino heterocycles), some azo and hydrazo compounds such as (147) have been obtained.

It has been shown¹¹⁴ that amino groups in the α - and γ -positions to an N-oxide group do not exist in the imino form [e.g. (148)], but are stabilised as amino groups which form comparatively stable diazonium salts.

Alkoxy, aryoxyl and arylthio groups at the α - and γ -positions to an N-oxide group are activated towards substitution by amines.

Hydroxyl groups at the α - or γ -positions of pyridine N-oxides form a prototropic system with the N-oxide group and there is the possibility of two tautomeric forms [e.g. 4-hydroxypyridine 1-oxide (149) or 1-hydroxy-4-pyridone (150)].



It has been shown for the equilibrium (149) \rightleftharpoons (150) that both forms are present in approximately equal amounts,¹¹⁵ but for 2-hydroxypyridine 1-oxide (151), Shaw¹¹⁶ showed that 1-hydroxy-2-pyridone (152) was the predominant tautomer.

β -Hydroxypyridine 1-oxides, however, exist in the hydroxy form (153) because the tautomeric form (154) is zwitterionic.

1.5. Conclusion

Heterocyclic N-oxides are valuable and widely used as intermediate products in the synthesis of various heterocyclic derivatives, some of which have been described. Although much work has been done, the field of heterocyclic N-oxide chemistry is still expanding rapidly.

The following thesis is concerned with studies on the synthesis and reactivity of benzo-1,2,4-triazine, quinoxaline and oxazole N-oxides. Particular emphasis has been placed on the study of the scope and mechanism of the nucleophilic substitution and 1,3-dipolar cycloaddition reactions of these types of heterocyclic N-oxide.

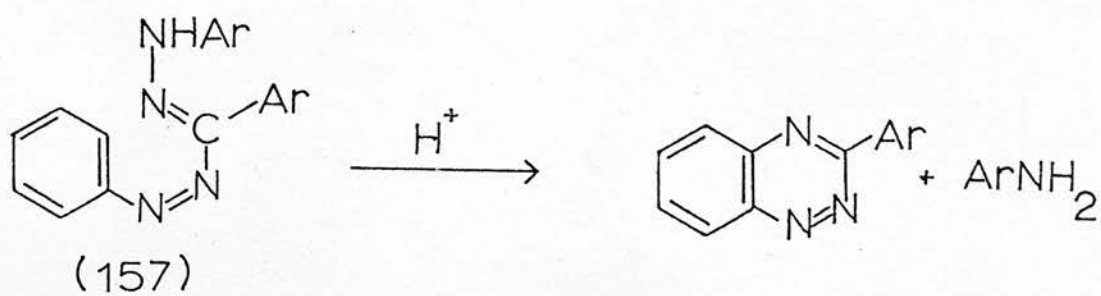
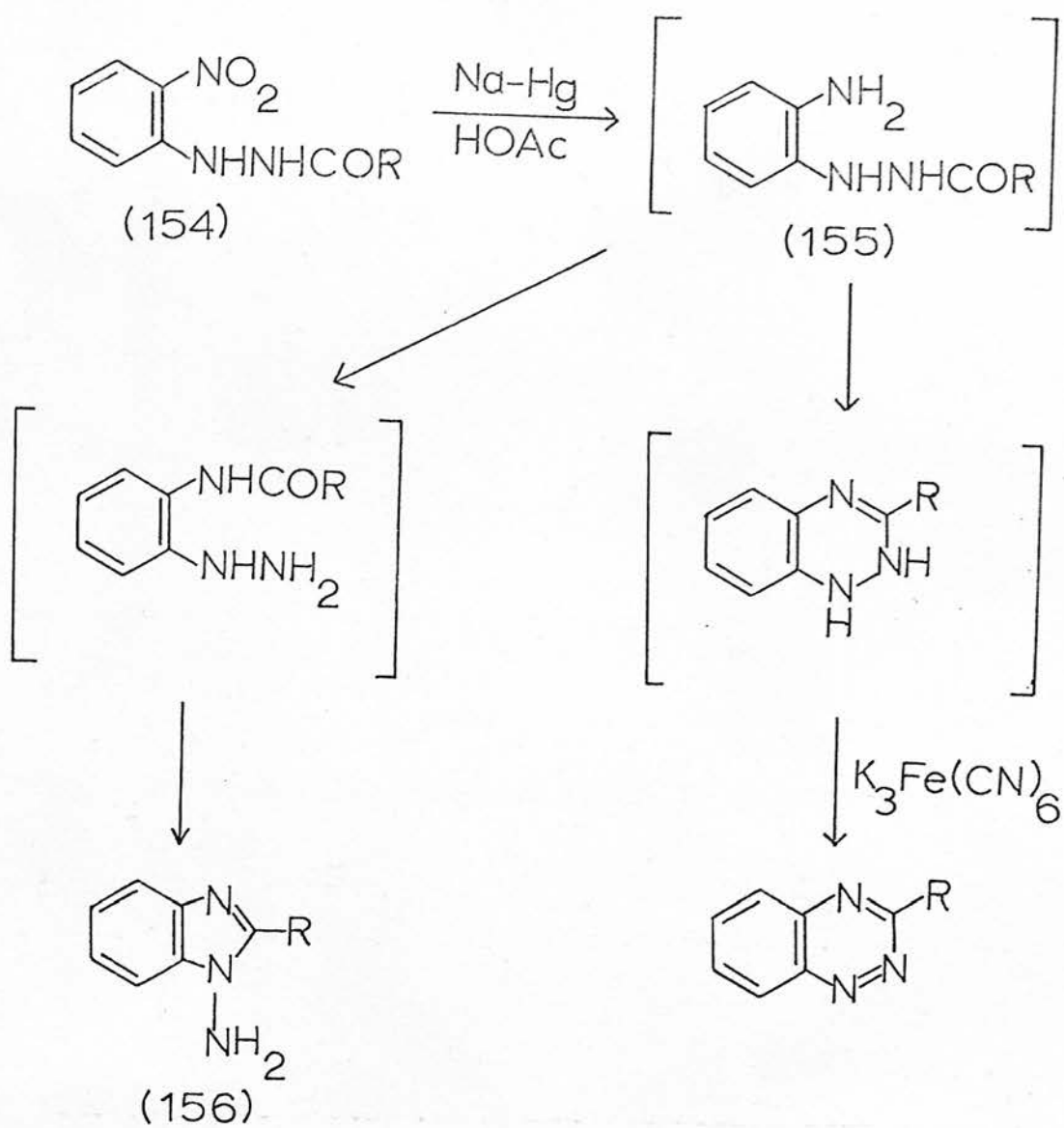
SECTION ONE

PART TWO

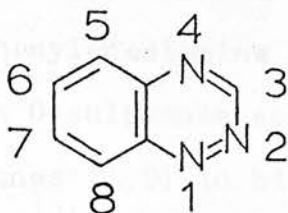
SOME STUDIES IN DISCUSSION TRIAZINE N-OXIDE CHEMISTRY

SECTION ONE

SOME STUDIES IN BENZO-1,2,4-TRIAZINE N-OXIDE CHEMISTRY



SOME STUDIES IN BENZO-1,2,4-TRIAZINE N-OXIDE CHEMISTRY

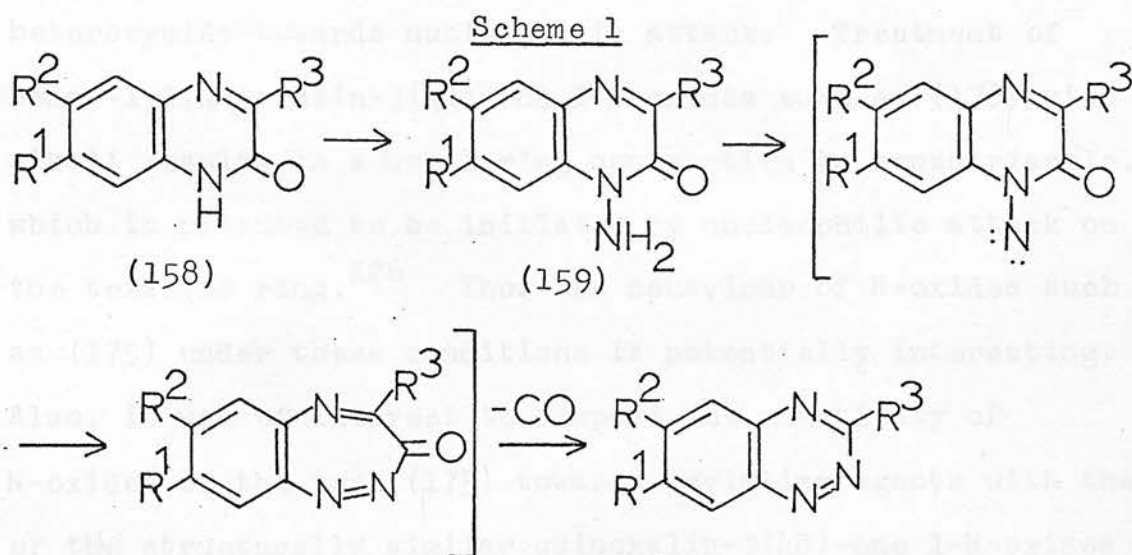


BENZO-1,2,4-TRIAZINE

The chemistry of benzo-1,2,4-triazine N-oxides has been relatively little explored. The lack of interest in these compounds can be attributed partly to the comparatively few suitable methods of synthesis of the benzo-1,2,4-triazine ring system and also presumably to the absence of benzo-1,2,4-triazines in nature. Possibly the only stimulus for the study of benzo-1,2,4-triazine N-oxides was the discovery that certain derivatives possess antimalarial activity.¹¹⁷

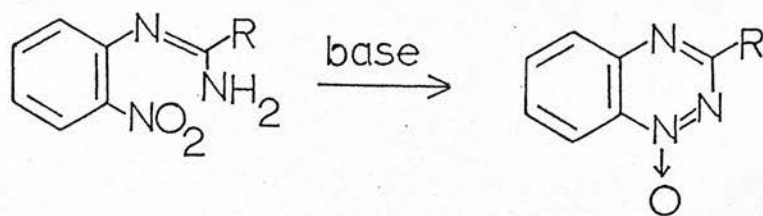
Benzo-1,2,4-triazines have long been available by two main synthetic routes. The Bischler reaction¹¹⁸ involves reductive cyclisation of *o*-nitrophenylhydrazides (154). However this method has the disadvantage that the intermediate N-acyl-N'-(*o*-aminophenyl)-hydrazines (155) can undergo acyl group migration and subsequent cyclisation to 1-aminobenzimidazoles (156). Recent variations¹¹⁹ of the Bischler reaction have been more successful. The Bamberger synthesis¹²⁰ of 3-arylbenzo-1,2,4-triazines involves the acid-catalysed cyclisation of formazans (157). Although well documented, both of these synthetic routes employ relatively inaccessible starting materials and are often difficult to reproduce. However, recently Rees and his coworkers¹²¹ have described

a simple, general route to benzo-1,2,4-triazines. Amination of quinoxalin-2(1H)-ones (158) (readily available by condensing an *o*-phenylenediamine with an α -keto acid or ester) with hydroxylamine O-sulphonic acid affords the 1-amino-quinoxalin-2(1H)-ones (159) in high yield. Oxidation of the latter compounds with lead tetraacetate affords benzo-1,2,4-triazines in good yields, possibly by the mechanism shown (Scheme 1).



This novel general method should make the benzo-1,2,4-triazine ring system more readily accessible.

Benzo-1,2,4-triazines obtained by any of these methods can be oxidised by peracids to the corresponding N-oxides. The most direct route to benzo-1,2,4-triazine 1-N-oxides is the base-catalysed cyclisation of *o*-nitroarylbenzamidines (160; R = Ar), ureas (160; R = OH), thioureas (160; R = SH), or guanidines (160; R = NH₂), a method which has been widely applied.^{117,119,122-5}

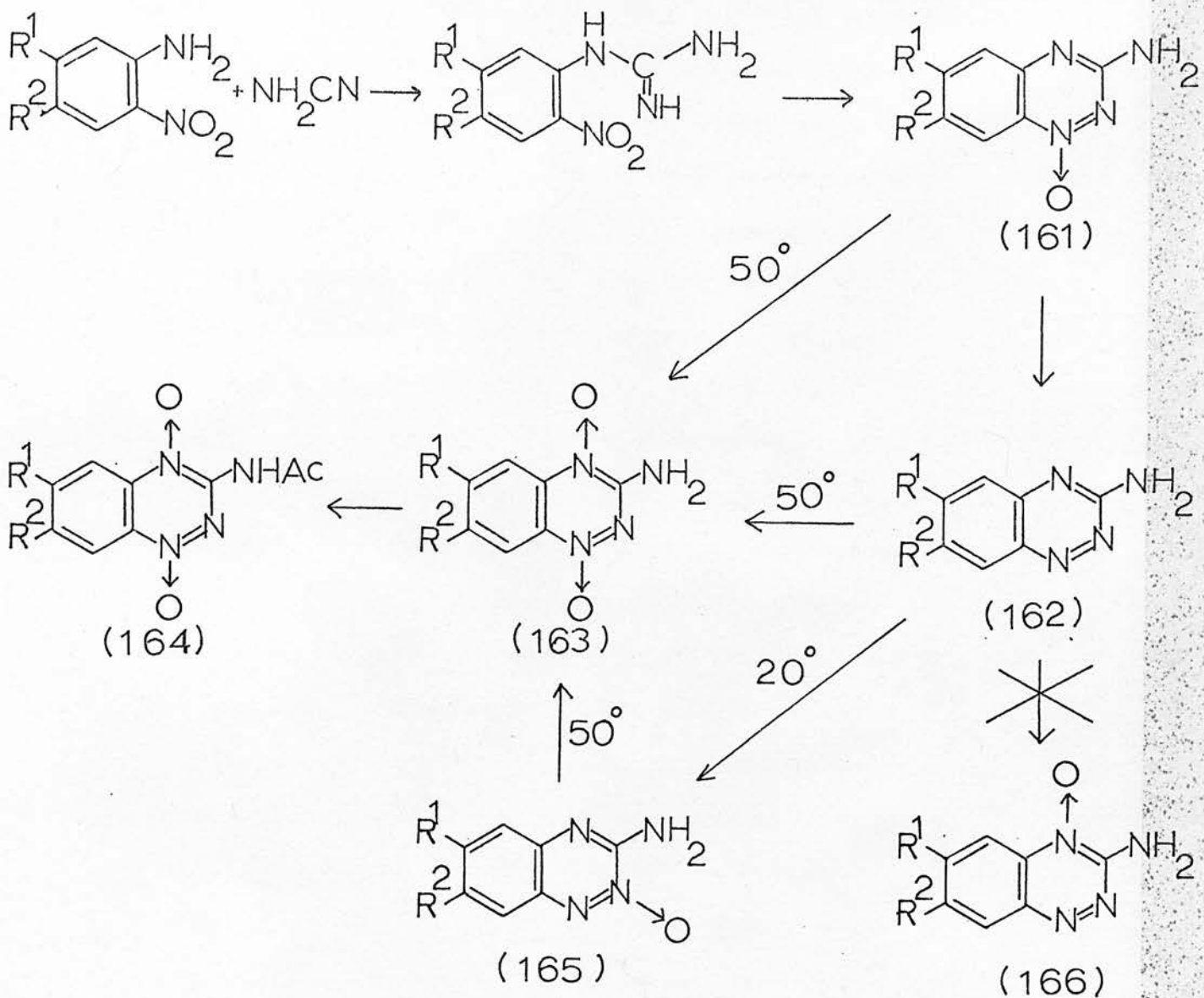


(160)

Our studies in the chemistry of benzo-1,2,4-triazine N-oxides were prompted by an interest in the reactivity of such heterocycles towards nucleophilic attack. Treatment of benzo-1,2,4-triazin-3(4H)-one 1-N-oxides such as (176) with alkali results in a novel ring contraction to benzotriazole, which is presumed to be initiated by nucleophilic attack on the triazine ring.¹²⁶ Thus the behaviour of N-oxides such as (175) under these conditions is potentially interesting. Also, it was of interest to compare the reactivity of N-oxides of the type (175) towards acylating agents with that of the structurally similar quinoxalin-3(4H)-one 1-N-oxides (202) (see Section 2). Since benzo-1,2,4-triazine N-oxides other than the 1-N-oxides were required for study we were initially confronted by a synthetic problem. Apart from the 1-N-oxide synthesis already mentioned no methods were available for the preparation of such molecules, and it was decided to evaluate peracid oxidation as a potential synthetic route.

Few studies have been made of the peracid oxidation of the benzo-1,2,4-triazine ring system. Oxidation of a benzo-1,2,4-triazine can, a priori, occur at either N(1), N(2), or N(4) yielding several mono- and di-N-oxides. Information

in the literature suggests that depending on the reaction conditions, both mono- and di-N-oxides are formed. Oxidation of 3-aminobenzo-1,2,4-triazine (162a) and some of its derivatives at 50° with hydrogen peroxide in acetic acid is reported¹²⁷ to yield a di-N-oxide formulated as the 1,4-di-N-oxide (163a). Similar oxidation at room temperature, on the other hand, yielded a mono-N-oxide, isomeric with the 1-N-oxide (161a) of known structure. On the basis that further oxidation yielded the 1,4-di-N-oxide (163a), this product was assigned¹²⁷ the 4-N-oxide structure (166a). Arndt,¹²⁴ however, had previously proposed the 2-N-oxide structure (165a) for this compound. Because of these conflicting reports it was considered worthwhile to reinvestigate the peracid oxidation of 3-aminobenzo-1,2,4-triazines to attempt to elucidate the structures of the N-oxides obtained. In theory the site of N-oxidation in a polyazaheterocycle can be established by a study of the dipole moments of the N-oxide products, but this method is often difficult in practice. However, a study of the proton chemical shift differences between the N-oxides and the parent bases can be used to establish the site of N-oxidation. Thus peracid oxidation of the 3-aminobenzo-1,2,4-triazines (162) and their 1-N-oxides (161) was carried out and the products isolated were examined by n.m.r. spectroscopy. It can be shown, in general, that prolonged oxidation at room temperature gives rise almost exclusively to the 2-N-oxides (165) whereas oxidation at 50° yields the 1,4-di-N-oxides (163). Representative i.r. spectra of 3-aminobenzo-1,2,4-triazine (162) and its N-oxides (Figures 10-14) are collected at the end of this section.



	R^1	R^2
(a)	H	H
(b)	H	CH_3
(c)	H	CH_3O
(d)	H	Cl
(e)	CH_3	CH_3

Table 1

Assignments^{a,b} (τ) of ¹H n.m.r. Resonance Signals of 3-Aminobenzo-1,2,4-triazines and their Mono- and Di-N-oxides.

Compound	H(5)	H(6)	H(7)	H(8)	OCH ₃	CCH ₃	COCH ₃	NH ₂
(161a)	2.21m ^c	1.86td	2.21m ^c	1.55dd	-	-	-	-
(161b)	2.33d	2.01dd	-	1.78s	-	7.39s	-	-
(161c)	2.24m ^d	2.24m ^d	-	2.24m ^d	5.97s	-	-	-
(161d)	2.23d	1.94dd	-	1.65d	-	-	-	-
(161e)	2.45s	-	-	1.82s	-	7.40s) 7.46s)	-	-
(162a)	2.13m ^c	1.74m ^e	2.13m ^c	1.74m ^e	-	-	-	-
(162b)	2.26d	1.87dd	-	2.03s	-	7.35s	-	-
(162c)	2.28d	2.04dd	-	2.77d	5.91s	-	-	-
(162d)	2.24dd	(1.90)	-	(1.79)	-	-	-	-
(162e)	2.39s	-	-	2.09s	-	7.31s) 7.43s)	-	-
(165a)	2.21m ^c	1.99m ^e	2.21m ^c	1.99m ^e	-	-	-	-
(165b)	2.30d	2.13dd	-	2.19s	-	7.39s	-	-
(165c)	2.25m ^f	2.25m ^f	-	2.68s	5.96s	-	-	-
(165d)	2.30d	2.12m ^e	-	2.12m ^e	-	-	-	-
(165e)	2.36s	-	-	2.20s	-	7.38s) 7.45s)	-	-
(163a)	1.91dd	1.71td	2.16td ^g	1.56dd	-	-	-	2.16 ^g
(163b)	1.96s ^f	1.96s ^f	-	1.75s	-	7.36s	-	2.32
(163c)	1.92s	2.13dd	-	2.25d	5.95s	-	-	2.46
(163d)	1.89s ^f	1.89s ^f	-	1.61s	-	-	-	2.21
(163e)	2.11s	-	-	1.81s	-	7.35s) 7.45s)	-	2.37
(164a)	←	1.38 - 2.26m ^h	←	←	-	-	7.34s	-
(164b)	←	1.47 - 1.91m ^d	←	←	-	←(7.29s) (7.33s)→	→	-
(164c)	1.59d	2.08dd	-	2.20d	5.90s	-	7.36s	-
(164d)	1.54m ⁱ	1.82dd	-	1.54m ⁱ	-	-	7.37s	-
(164e)	1.76s	-	-	1.71s	-	←(7.31s) (7.33s)→ (7.37s)	→	-

^a Spectra taken at 100 MHz on a Varian HA100 instrument in trifluoroacetic acid at 28° with tetramethylsilane as internal standard. Chemical shifts are given in p.p.m. down-field from tetramethylsilane to centre of multiplets and are measured to an accuracy of ± 0.01 p.p.m.; s = singlet; d = doublet; dd = double doublet; td = triple doublet; m = multiplet.

^b J_{5,6} and J_{6,8} were in the ranges 7.5-9.4 and 1.3-2.5 Hz respectively.

^c H(5) - H(7). ^d H(5) - H(6) - H(7). ^e H(6) - H(8). ^f H(5) - H(6).

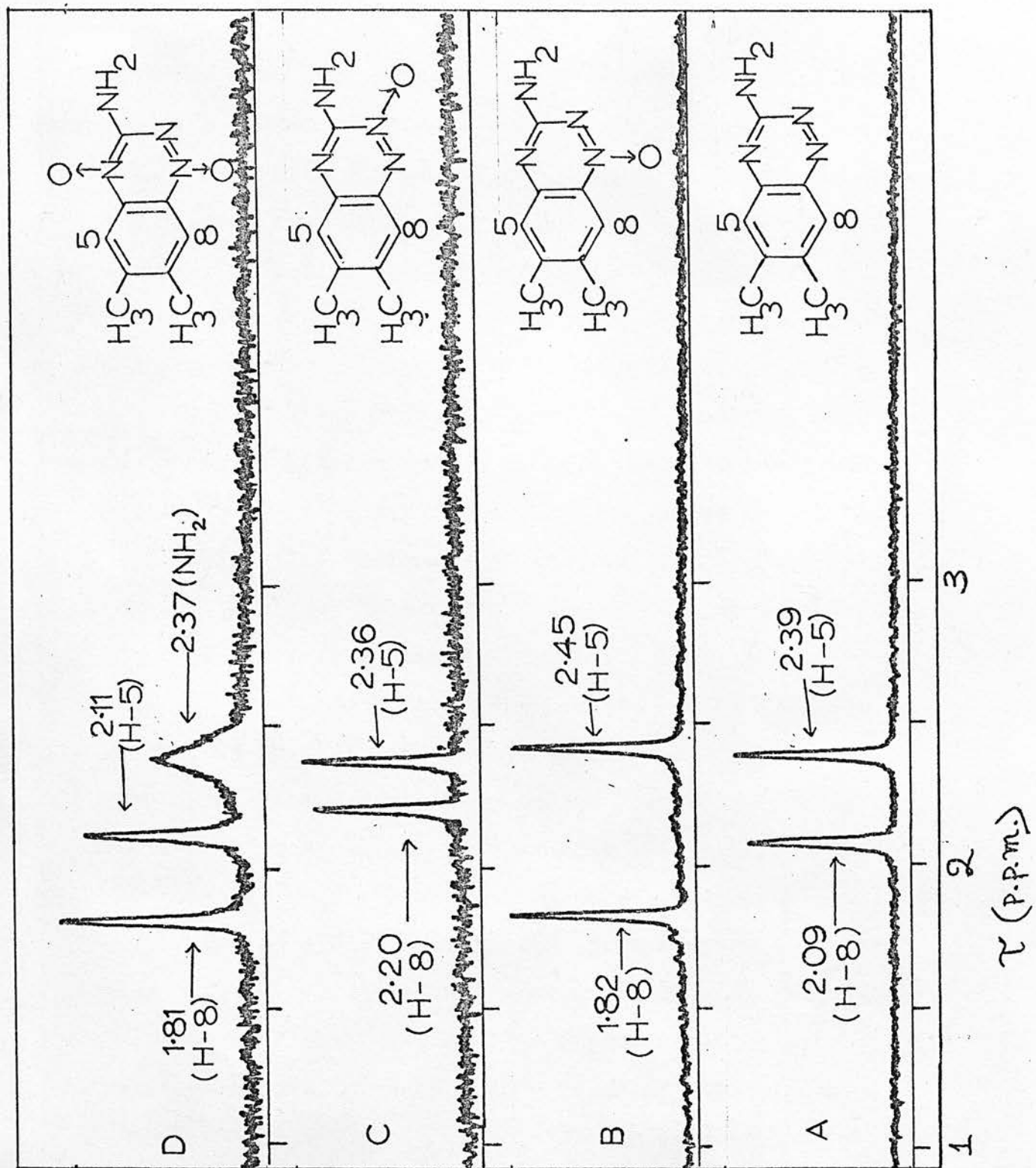
^g H(7) - NH₂. ^h H(5) - H(6) - H(7) - H(8). ⁱ H(5) - H(8).

Figures in parentheses denote approximate values.

The condensation^{117,123} of o-nitroaniline derivatives with cyanamide provided a convenient route to the 3-amino-benzo-1,2,4-triazine 1-N-oxides (161), in which the position of the N-oxide group is known with certainty. In contrast to previous reports^{117,123} the best yields were obtained using twofold quantities of cyanamide. Dithionite reduction smoothly converted these 1-N-oxides (161) in high yield into the parent 3-aminobenzo-1,2,4-triazines (162).

The site of N-oxidation or quaternisation in nitrogen-containing heterocycles can be determined by a study of the changes in chemical shift of protons in the neighbourhood of the reaction site. The downfield shift of H(8) in cinnoline 1-N-oxide compared with cinnoline is due to the deshielding effect of the N-oxide group.^{128,129} This effect is readily shown by the chemical shift data (Table 1) obtained from the ¹H n.m.r. spectra of the 3-aminobenzo-1,2,4-triazines (162) and their 1-N-oxides (161). The complexity of the splitting pattern in the ¹H n.m.r. spectrum of the unsubstituted compounds (161a) (Figure 6) and (162a) (Figure 7) precluded unambiguous first-order assignment of the peaks. For this reason, the dimethyl derivatives (161e) and (162e), which give rise to a much simpler situation where the spectra (Figure 1) are uncomplicated by spin-spin splitting, were studied initially (no attempt was made to detect CH₃-H splitting). The lower of the two signals is attributable to H(8) which is more deshielded in benzo-1,2,4-triazines than H(5).¹³⁰ This is confirmed by the downfield shift (ca. 0.2 p.p.m.) of H(8) observed for

Figure 1. ^1H n.m.r. spectra of compound (162e) A, (161e) B, (163e) C, and (165e) D, (trifluoroacetic acid; 100 MHz).



the 1-N-oxide compared with the parent heterocycle. In contrast, the peak at higher field due to H(5) shows little change (Tables 1 and 2).

Comparison of the ^1H n.m.r. spectra of the mono-substituted benzo-1,2,4-triazines (162b-d) and their 1-N-oxides (161b-d) also demonstrates the marked downfield shift in the signal due to H(8) produced by the N-oxide group. The ^1H n.m.r. spectra of the monosubstituted benzo-1,2,4-triazines (162b-d) and their 1-N-oxides (161b-d) are complicated by spin-spin splitting in an ABX system (e.g. Figures 2 and 3). However, first-order analysis of the splitting pattern permitted the assignment of the proton resonances in the spectra of compounds (161b), (161d) and (162b-c) (Table 1). These assignments are supported by the magnitudes of the coupling constants (footnote to Table 1) also obtained by first-order analysis. Individual chemical shifts and coupling constants were unobtainable for the 1-N-oxide (161c) because of the merging of the signals into a multiplet, spread over only 0.09 p.p.m. For the chloro-compound (162d) the signal due to H(8) overlapped with the lower half of the signal due to H(6) precluding accurate assignment of these resonances. However, the signal due to H(5) was readily observable, as was the upper half of the signal due to H(6) and values for $J_{5,6}$ and $J_{6,8}$ could thus be obtained and hence approximate values can be assigned to the chemical shifts of H(6) and H(8).

The ^1H n.m.r. spectrum of the parent 1-N-oxide (161a) (Figure 6) consists of three groups of lines centred at

Table 2.

Effects of N-Oxidation on Proton Chemical Shifts.

Proton Shifts^a (p.p.m.) of 3-Aminobenzo-1,2,4-triazine
N-Oxides compared with the corresponding 3-Aminobenzo-
1,2,4-triazines (162).

Compound	H(5)	H(6)	H(7)	H(8)
(161a)	(+0.08)	(+0.12)	(+0.08)	(-0.19)
(161b)	+0.07	+0.14	-	-0.25
(161c)	(-0.04)	(0.20)	-	(-0.53)
(161d)	-0.01	(+0.04)	-	(-0.14)
(161e)	+0.06	-	-	-0.27
(165a)	(+0.08)	(+0.25)	(+0.08)	(+0.25)
(165b)	+0.04	+0.26	-	+0.16
(165c)	(-0.03)	(+0.21)	-	-0.09
(165d)	+0.06	(+0.22)	-	(+0.33)
(165e)	-0.03	-	-	+0.11
(163a)	(-0.22)	(-0.03)	(+0.03)	(-0.18)
(163b)	-0.30	+0.09	-	-0.28
(163c)	-0.36	+0.09	-	-0.52
(163d)	-0.35	(-0.01)	-	(-0.18)
(163e)	-0.28	-	-	-0.28
(164a)	-	-	-	-
(164b)	(-0.35) ^b	(+0.04) ^b	-	(-0.12) ^b
(164c)	-0.69	+0.04	-	-0.57
(164d)	(-0.70)	(-0.08)	-	(-0.25)
(164e)	-0.63	-	-	-0.38

^a Values in parentheses are approximate

^b Minimum approximate values

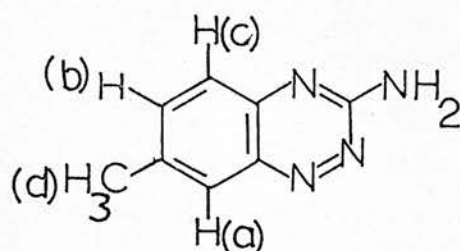
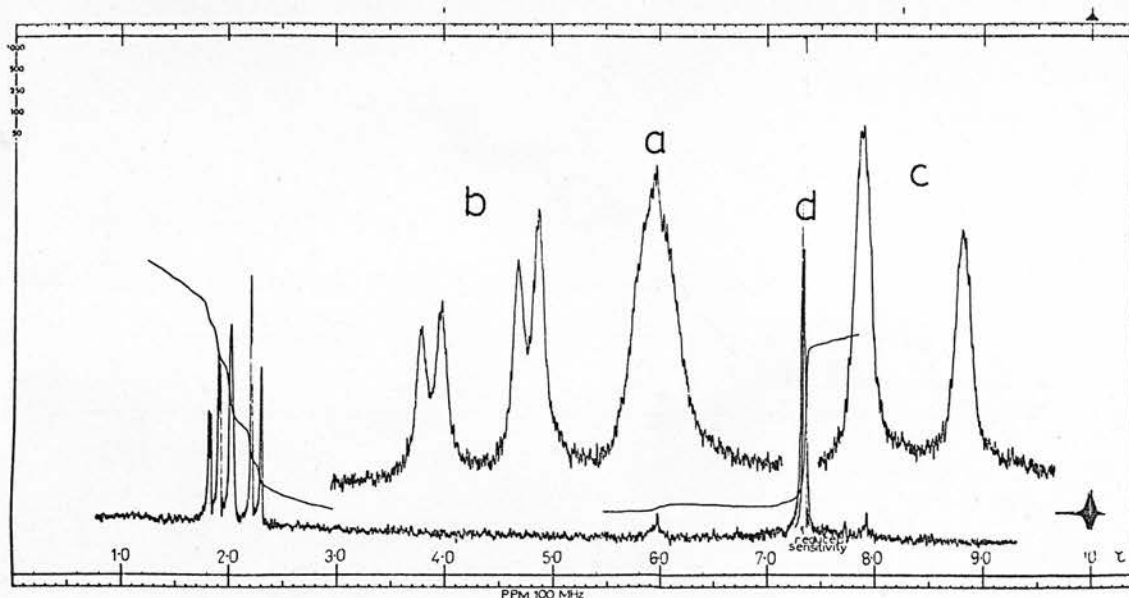


Figure 2.

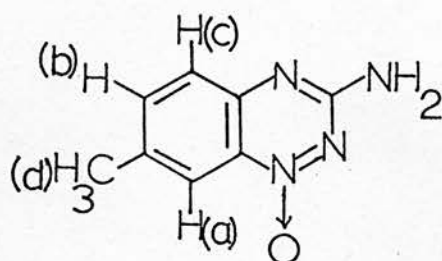
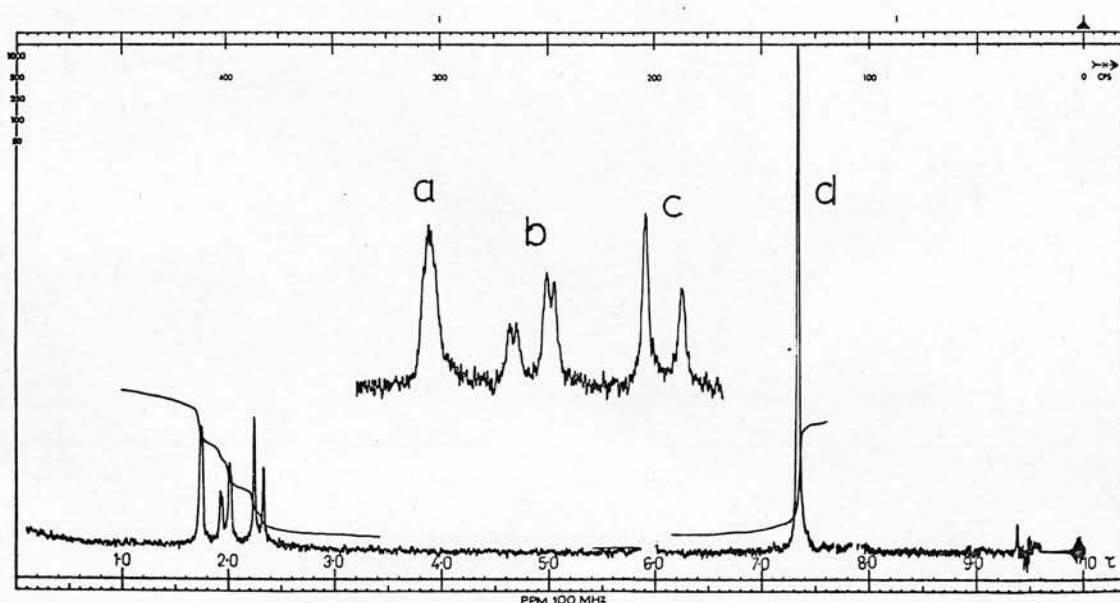


Figure 3.

^1H n.m.r. spectra of compounds (162b) (Figure 2) and (161b) (Figure 3) in trifluoroacetic acid at 100 MHz; inset expansions to 250 Hz.

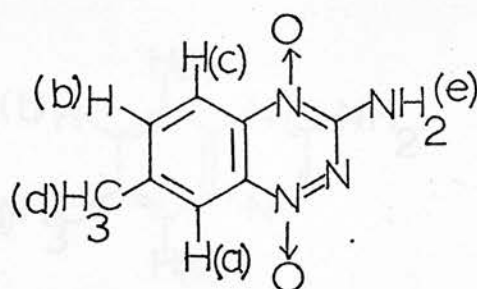
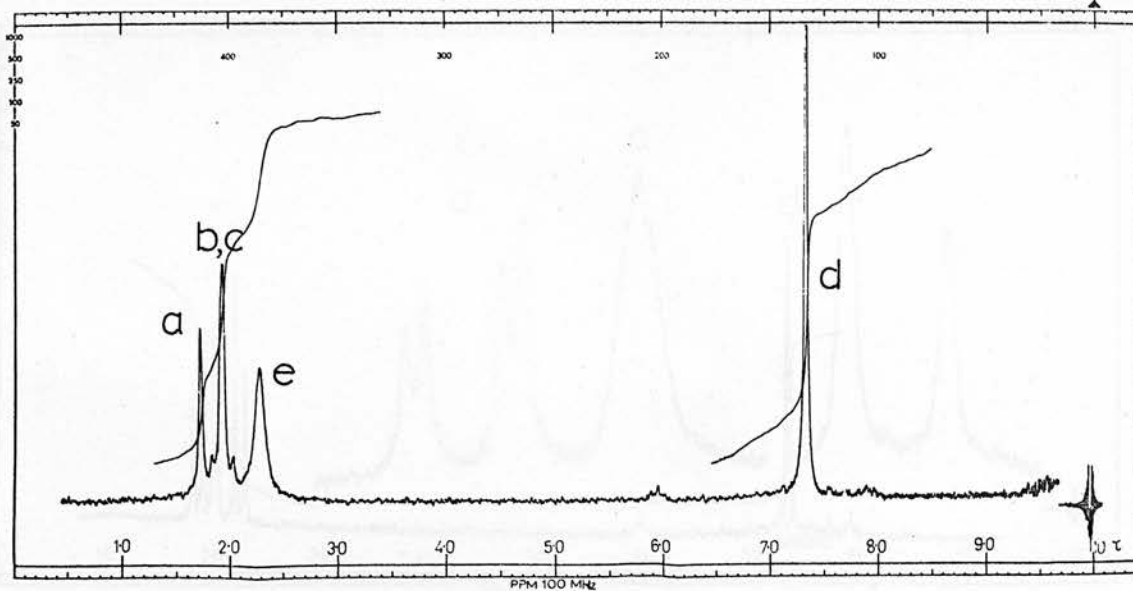


Figure 4 .

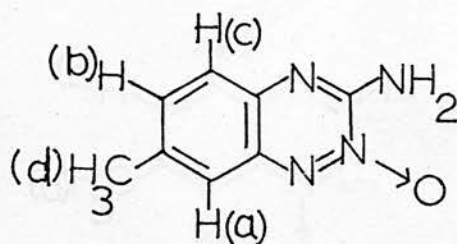
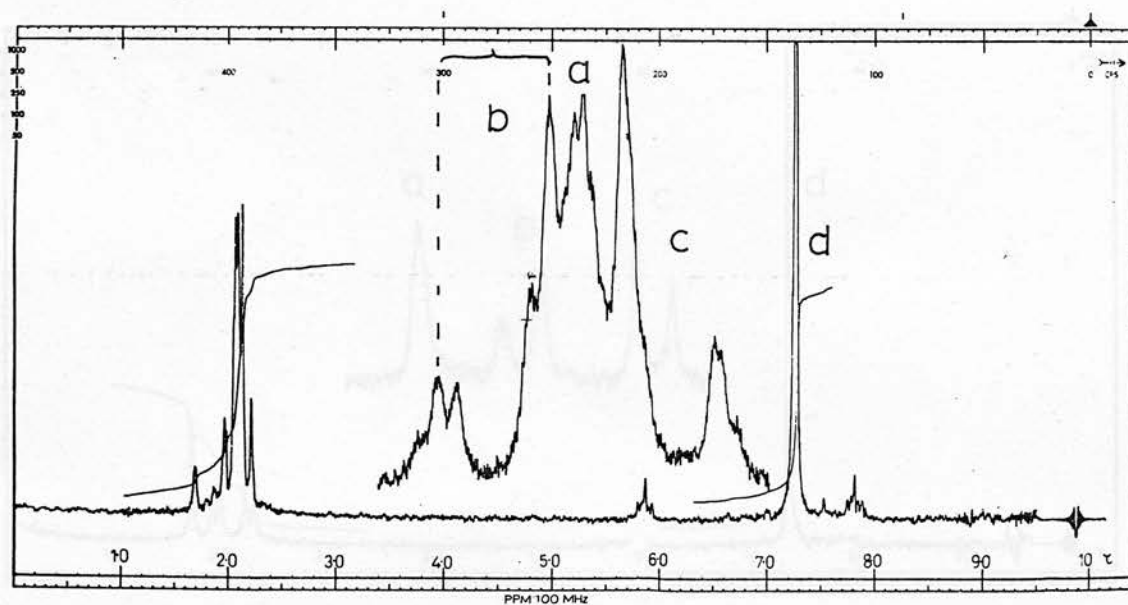


Figure 5 .

¹H n.m.r. spectra of compounds (163b) (Figure 4) and (165b) (Figure 5) in trifluoroacetic acid at 100 MHz; inset expansions to 250 Hz.

τ 1.55, 1.86 and 2.21 in the integrated ratio of 1:1:2. The chemical shift of H(8) ought to be lowest owing to the deshielding effect of the 1-N-oxide group. The mesomeric effect of the 3-amino group should increase the π -electron density at C(5) and C(7) and thus H(6) ought to be less shielded than H(5) and H(7). On the basis of this reasoning the proton resonances are assigned as shown (Figure 6 and Table 1). These assignments are substantiated by the observed splitting pattern and the coupling constants (footnote to Table 1) obtained by first-order analysis. The ^1H n.m.r. spectrum of the parent benzo-1,2,4-triazine (162a) (Figure 7) is further complicated by the merging of the two lowest proton resonances, and consists of two groups of lines centred at τ 1.74 and τ 2.13 in the integrated ratio 2:2. These are attributed to H(8) - H(6) and H(5) - H(7) respectively, as shown (Figure 7 and Table 1) on the basis of the splitting pattern and measurable coupling constants. However the complexity of the spectrum precluded the accurate determination of individual chemical shifts.

Despite the more complex nature of the spectra of compounds (161a-d) and (162a-d) it can be clearly seen from the data in Table 1 that compared with H(5) and H(8) in the parent benzo-1,2,4-triazines (162), the chemical shift of H(5) in the N-oxides (161) remains constant to within \pm (0.02 - 0.08) p.p.m. whereas H(8) experiences a downfield shift of the order 0.14 - 0.53 p.p.m. (Table 2). These results establish conclusively the deshielding effect experienced by the peri hydrogen atom -H(8)- of the

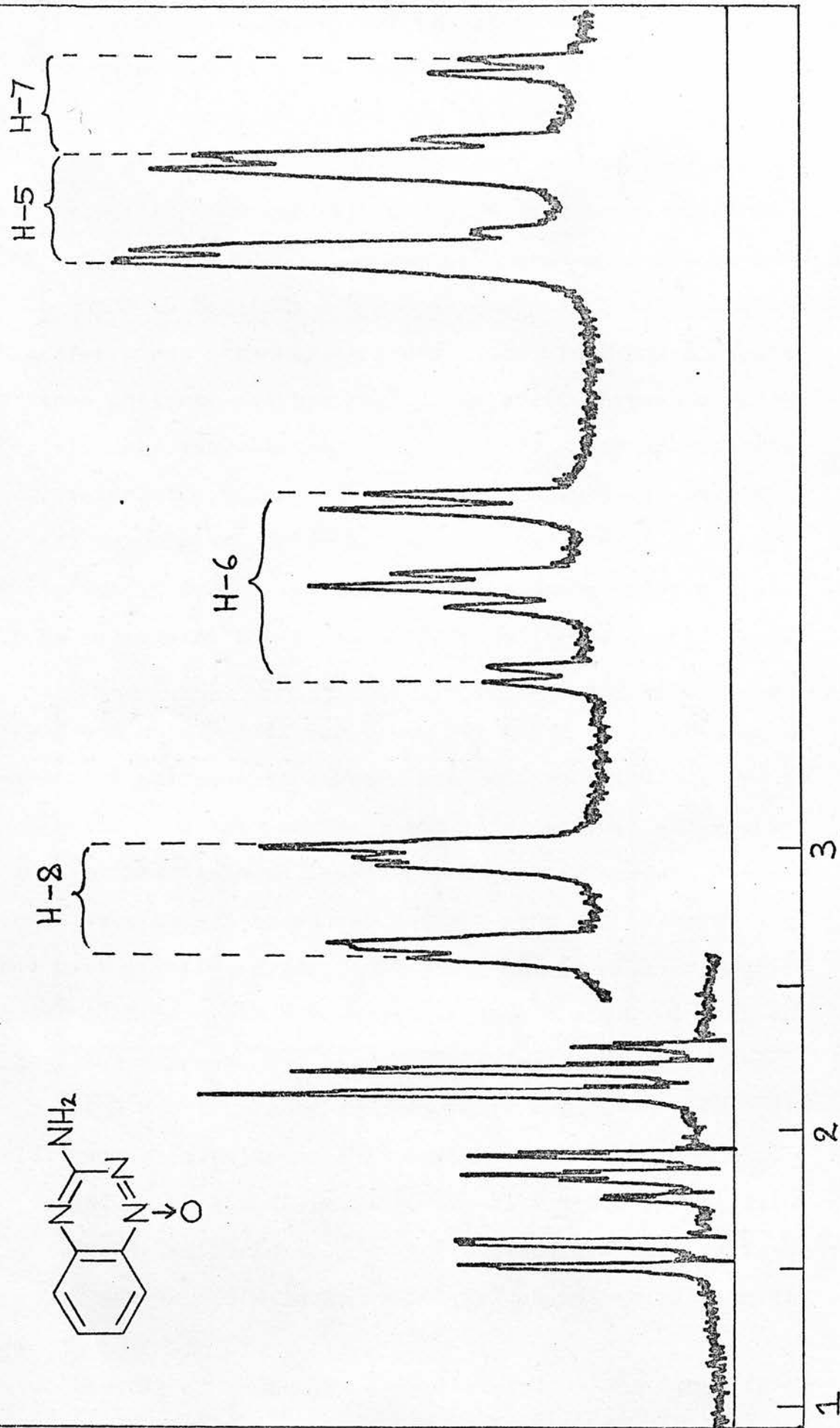
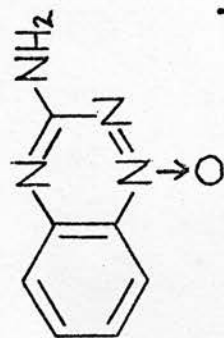


Figure 6. τ (p.p.m.)

^1H n.m.r. spectrum of compound (161a) (trifluoroacetic acid; 100 MHz; inset expansion to 250 Hz).

benzo-1,2,4-triazine ring due to an adjacent 1-N-oxide group.

Prolonged peracid oxidation of the 1-N-oxides (161a-e) afforded orange-red products in high yield, which analysed correctly as di-N-oxides. The compounds obtained by Robbins and Schofield¹²⁷ by oxidation of the 1-N-oxides (161a) and (161c-d), however, differed appreciably in m.p. from those obtained in the present investigation. Evidence for the di-N-oxide structures was provided by the presence of strong (P-16) and (P-32) peaks in the mass spectra⁶⁰ of these compounds. No attempt was made to analyse the fragmentation patterns or to assign the positions of N-oxidation by the relative strengths of the peaks although this method has been applied to the elucidation of the structures of 1,2,4-triazine N-oxides.^{131,132} The presence of a 1-N-oxide group and the retention of the benzo-1,2,4-triazine nucleus in the di-N-oxides was demonstrated by the controlled dithionite reduction of the di-N-oxide (163a) to the 1-N-oxide (161a). On the basis of the foregoing evidence the di-N-oxides must be 1,4- or 1,2-derivatives. The presence of a 4-N-oxide group rather than a 2-N-oxide group is shown by the chemical shift data (Table 1) for the di-N-oxides, thus establishing their formulation as the 1,4-di-N-oxides (163).

The marked downfield shift of H(5) and the essentially static value for H(8) in the di-N-oxide (163e) (Figure 1 and Table 1) relative to the 1-N-oxide (161e) from which it is derived is strong evidence for a 1,4-di-N-oxide structure. In addition both H(5) and H(8) in compound

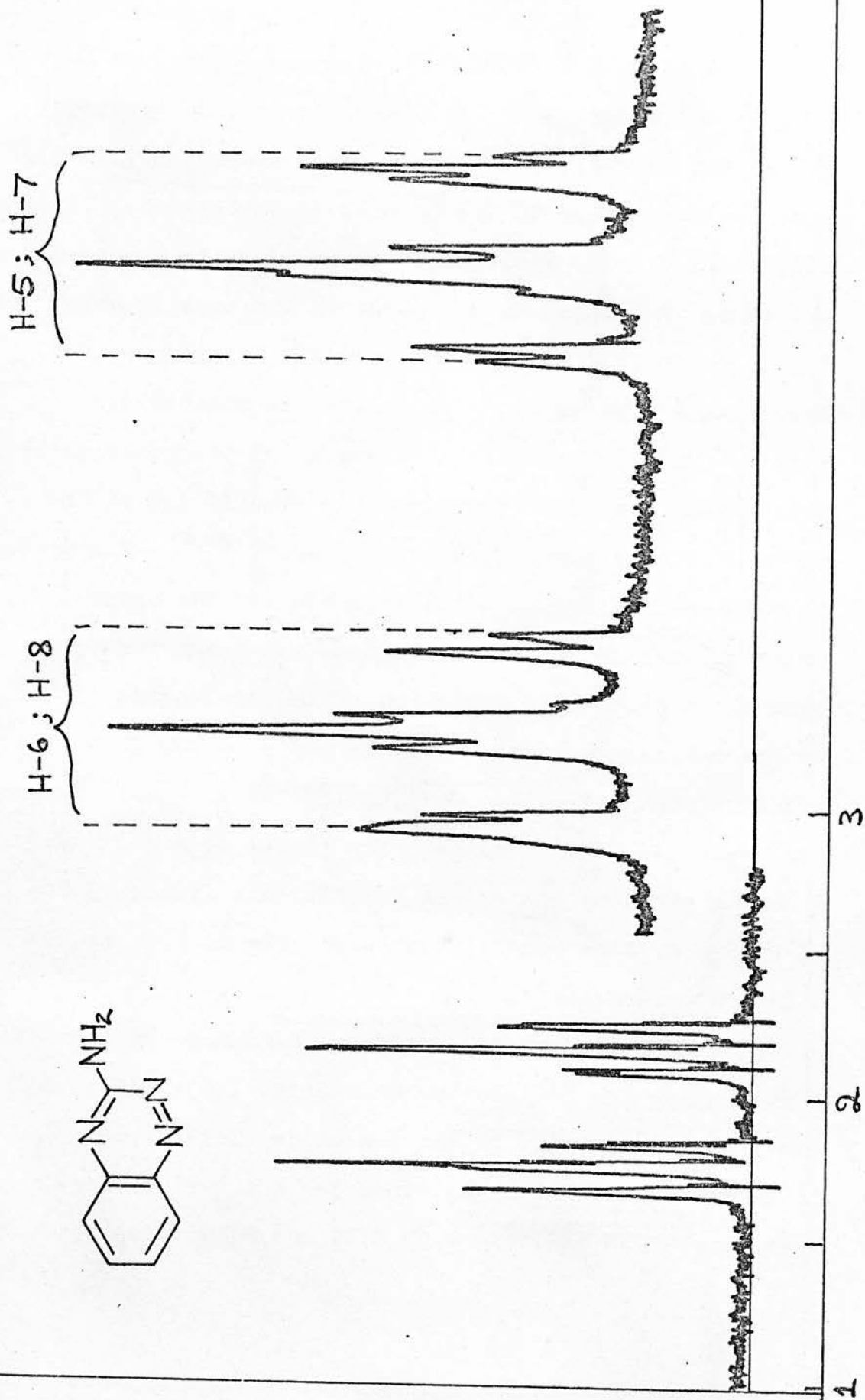
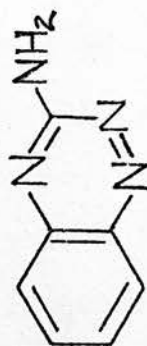
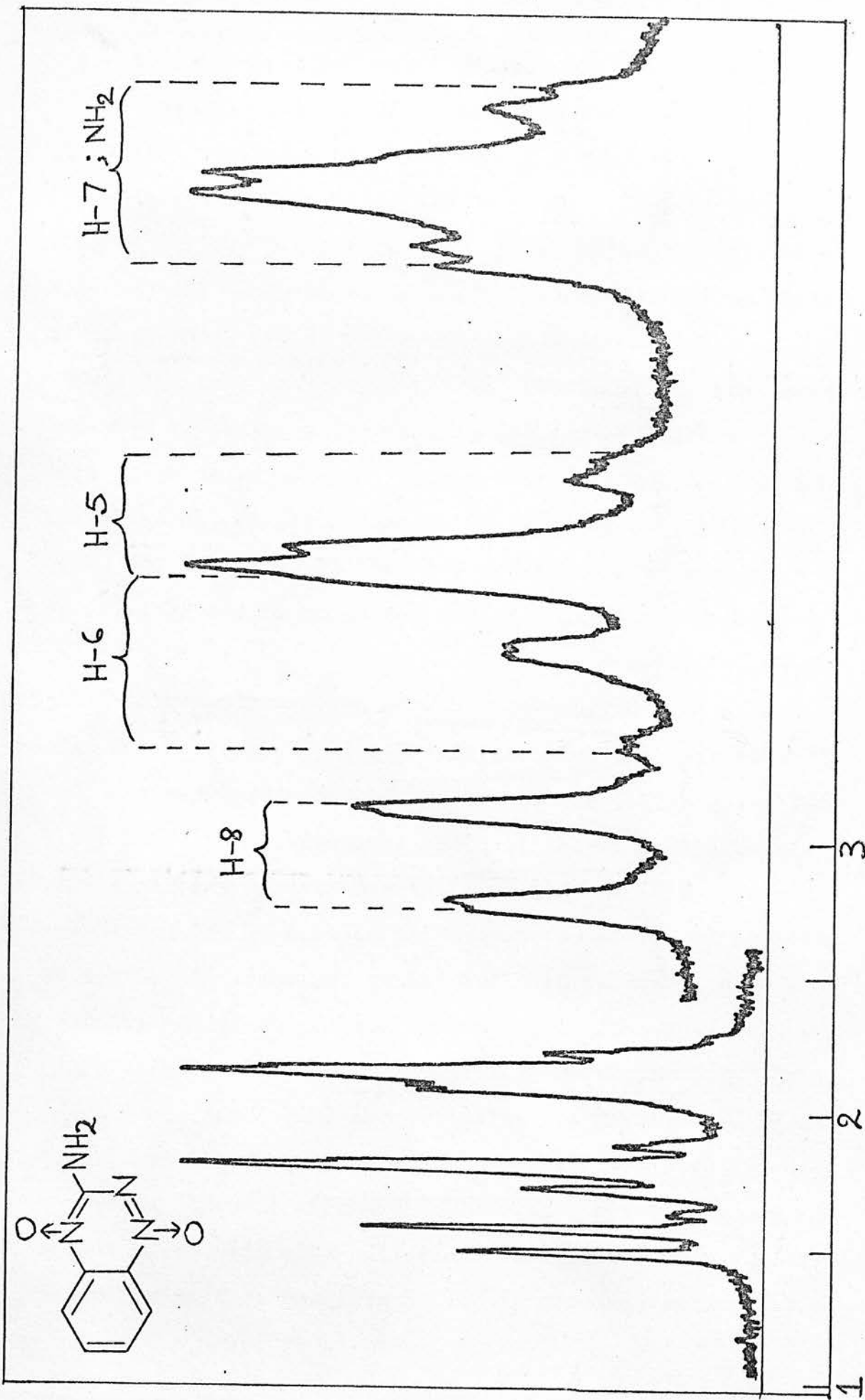


Figure 7. ^1H n.m.r. spectrum of compound (162a) (trifluoroacetic acid, 100MHz; inset expansion to 250 Hz).

(163e) appear at considerably lower field relative to H(5) and H(8) in the dimethylbenzo-1,2,4-triazine (162e), indicating that both N(1) and N(4) are oxidised. Since it is absent in the spectrum of the corresponding acetylamino derivative (164e)(Table 1), the broad signal at τ 2.37 in (163e) can be attributed to the amino group. The presence of a broad signal in the spectrum due to the amino group is presumably the result of the low rate of exchange of the amino-protons with trifluoroacetic acid, caused by hydrogen bonding with the 4-N-oxide group. The enhanced downfield shift of H(5) in the acetyl derivative (164e) (Tables 1 and 2) is a measure of the greater deshielding effect of the 4-N-oxide group resulting from the reduction in the basicity of the amino-centre.

The ^1H n.m.r. spectra of the monosubstituted di-N-oxides (163b-d) are more complex, and only in the case of the methoxy-di-N-oxide (163c) are all of the proton resonances readily assignable (see Table 1). The appearance of H(5) at lower field than H(8) in this compound and also in the benzo-1,2,4-triazine (162c) is not surprising because of the powerful shielding effect at H(8) induced by the mesomeric effect of the methoxy-group. The lack of resolution in the spectra of the di-N-oxides (163b)(Figure 4) and (163d) precluded assignment of chemical shifts to the individual protons. With the exception, again, of the methoxy-derivative (164c) the spectra of the acetylamino compounds (164b-d) showed little better resolution (Table 1). The high field signal in the chloro-compound (164d) is assigned to H(6) but other-



τ (p.p.m.)

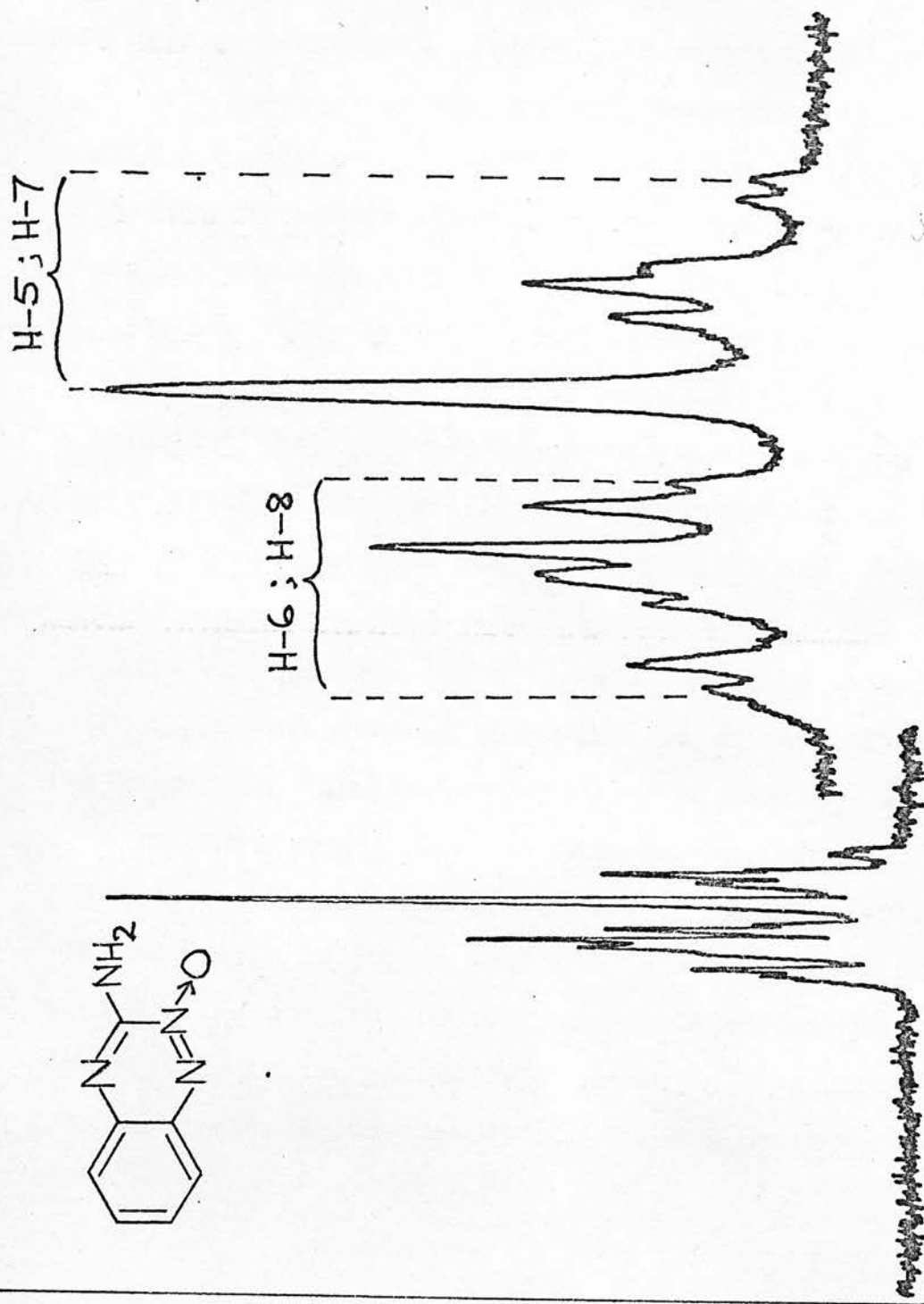
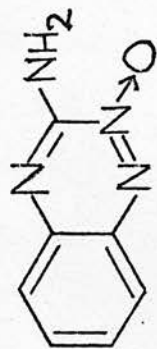
Figure 8. ^1H n.m.r. spectrum of compound (163a) (trifluoroacetic acid; 100 MHz; inset expansion to 250 Hz).

wise accurate values for chemical shifts and coupling constants for the aromatic protons in compounds (164b) and (164d) were not obtainable. The signal due to the amino group in the di-N-oxides (163b-d) is again absent in the acetyl derivatives (164b-d) and the downfield shift of H(5) is again enhanced in these compounds. Despite the lack of precision in measuring individual proton resonances, the general pattern again shows that relative to H(5) and H(8) in the benzo-1,2,4-triazines (162b-d) there is a marked downfield shift of H(5) in the di-N-oxides (163b-d). The observed downfield shift of H(5) in the di-N-oxides (163b-d) compared to the 1-N-oxides (161b-d), together with the close agreement of the chemical shift of H(8) in both classes of N-oxide is also very strong evidence for the proposed 1,4-di-N-oxide structures.

The ^1H n.m.r. spectrum of the di-N-oxide derived by peracid oxidation of the 1-N-oxide (161a) is shown in Figure 8. Despite its complexity, comparison with the spectra of compounds (161a) and (162a) and a consideration of the first-order splitting allows the proton resonances to be assigned as shown (Table 1). This interpretation is supported by the values of the coupling constants (footnote to Table 1) measured by first-order analysis. Comparison with the data for the 1-N-oxide (161a) (Table 1) shows that the 1,4-di-N-oxide formulation (163a) is correct. Thus the chemical shift of H(8) is similar to that in the 1-N-oxide (161a) (Tables 1 and 2) in accord with the presence of a 1-N-oxide group and the chemical shift of H(5) is further

downfield by ca. 0.22 p.p.m. than H(5) in the 1-N-oxide (161a) establishing the presence of a 4-N-oxide group.

Prolonged peracid oxidation of the 3-aminobenzo-1,2,4-triazines (162a) and (162c-d) at room temperature gave moderate to high yields of compounds which differed somewhat in m.p. from the products previously reported by Robbins and Schofield,¹²⁷ and by Arndt and Rosenau.¹²⁴ Similar oxidation of the benzo-1,2,4-triazines (162b) and (162e) afforded the corresponding methyl derivatives in high yield. All of these compounds were obtained pure after one crystallisation and analysed correctly as mono-N-oxides. The presence of the N-oxide group is further supported by the molecular weights of the oxidation products and the presence of strong (P-16) peaks in their mass spectra. These mono-N-oxides were different from the 1-N-oxides (161) of known structure (see before) as shown by the i.r. spectra of the unsubstituted compounds (161a) and (165a) (Figures 11 and 12). The oxidation products must therefore be 4-N-oxides (166) or 2-N-oxides (165), both structures having been proposed at different times.^{124,127} Again, the site of N-oxidation can be determined by a consideration of the ¹H n.m.r. spectra of these mono-N-oxides. As discussed above for the 1,4-di-N-oxides (163), the presence of a 4-N-oxide group in a benzo-1,2,4-triazine ring causes a downfield shift in the ¹H n.m.r. signal of H(5) relative to the unoxidised compound. On the other hand, a 2-N-oxide group would have no direct deshielding effect on H(5) and could only exert a smaller, transmitted, mesomeric effect.



9. τ (p.p.m.)

Figure 9. ^1H n.m.r. spectrum of compound (165a) (trifluoroacetic acid; 100 MHz; inset expansion to 250 Hz).

Although in some cases, the ^1H n.m.r. spectra of the crude mono-N-oxide products revealed traces of the 1-N-oxides (161), analysis of the spectra favoured the 2-N-oxide structure (165) rather than the 4-N-oxide structure (166).¹²⁷

In the ^1H n.m.r. spectrum of the dimethyl 2-N-oxide (165e) (Figure 1) the lower field signal is again attributed to H(8) and the similar position of H(5) (τ 2.36) compared with H(5) in the dimethylbenzo-1,2,4-triazine (162e) (τ 2.39) is strong evidence for the absence of a 4-N-oxide group and hence a 2-N-oxide structure.

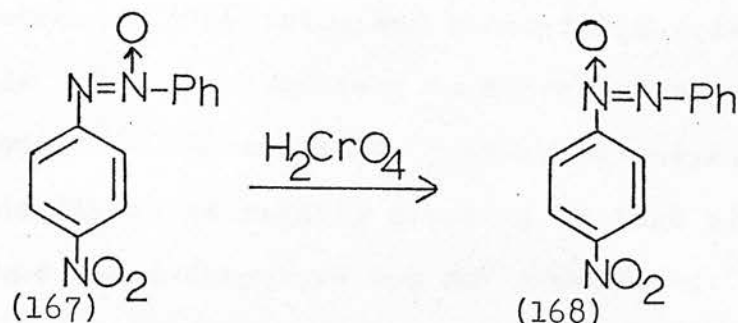
In the spectra of the mono-N-oxides, derived by oxidation of the monosubstituted benzo-1,2,4-triazines (162b-d), signal overlap prevented complete first order analysis of the splitting except in the case of the methyl compound (165b) (Figure 5), whose proton chemical shifts and coupling constants are as shown (Table 1). However, consideration of the splitting patterns permitted assignment of H(5) in the chloro-compound (165d) and of H(8) in the methoxy-compound (165c), although accurate chemical shifts and coupling constants could not be assigned to the other aromatic protons in these molecules. It is noticeable that the powerful shielding effect of the methoxy group again causes the signal due to H(8) to appear at higher field than H(5) in the 2-N-oxide (165c).

The ^1H n.m.r. spectrum of the mono-N-oxide derived from (162a) (Figure 9) proved, as expected, to be even more complex, but by comparison with the spectra of the compounds (161a), (162a) and (163a) (Figures 6, 7 and 8), the low field

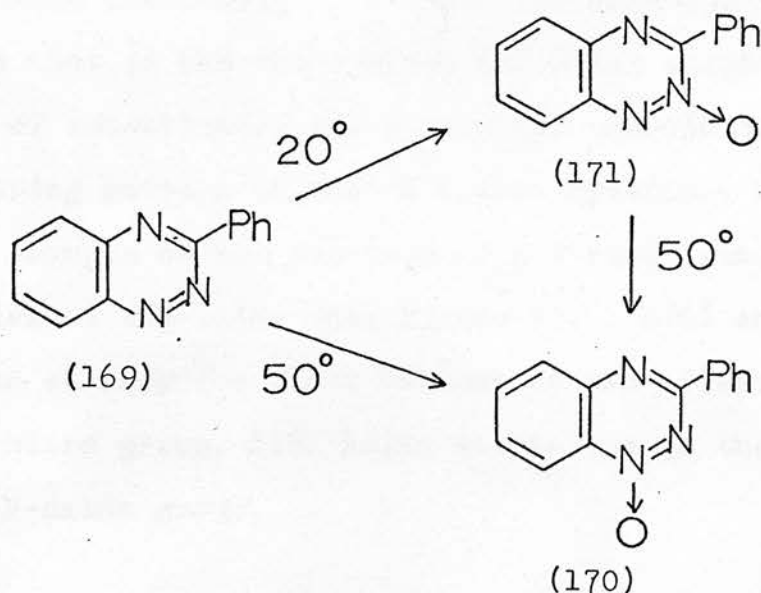
multiplet was assigned to H(6) - H(8) and the higher multiplet to H(5) - H(7). The main fact highlighted by this data (Table 1) is that there is a marked lack of a downfield shift of H(5) compared with the parent benzo-1,2,4-triazines (162). Thus a 4-N-oxide structure¹²⁷ is not possible and Arndt's original formulation of a 2-N-oxide structure¹²⁴ is correct. This is further supported by the observed upfield shift of H(8) and H(6) in the 2-N-oxides (165a-d) relative to the unoxidised benzo-1,2,4-triazines (162a-d) (Table 2). This may be attributed to an increase in π -electron density at C(6) and C(8) induced by the mesomeric effect of the 2-N-oxide group. A similar shielding effect has been observed in cinnoline 1-N-oxide.¹³¹

The observation by Robbins and Schofield¹²⁷ that peracid oxidation of 3-aminobenzo-1,2,4-triazine (162a) and 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a) also afforded the 1,4-di-N-oxide (163a) has been confirmed but the yields are poorer than for the oxidation of the 1-N-oxide (161a). They assumed, however, that the conversion of the mono-N-oxide, isomeric with the 1-N-oxide, into the 1,4-di-N-oxide was simply a second oxidation step. This assumption has now been shown to be incorrect as the compound in question is a 2-N-oxide and not a 4-N-oxide. The conversion of the 2-N-oxide (165a) into the 1,4-di-N-oxide (163a) could possibly be occurring by deoxygenation followed by reoxidation at a different centre. This process, although uncommon, has a precedent.⁵¹ (See Introduction, page 18). A second, more likely possibility is that a migration of oxygen occurs as

observed in the rearrangement of azoxybenzene derivatives. Thus β -p-nitroazoxybenzene (167) is converted into the α -isomer (168) on treatment with chromic acid.¹³³ An attempt to convert the 2-N-oxide (165a) into the 1-N-oxide (161a) with perchloric acid was unsuccessful.

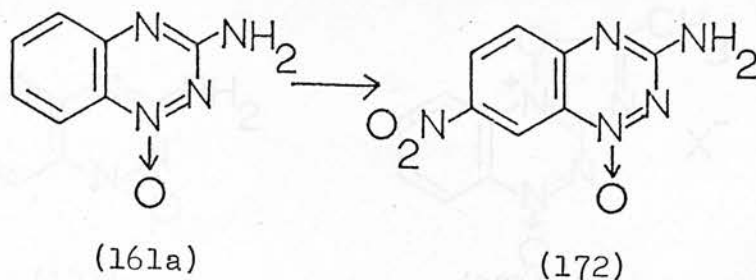


Robbins and Schofield¹²⁷ claim to have found an instance of this type of migration in heterocyclic N-oxides. They reported that peracid oxidation of 3-phenylbenzo-1,2,4-triazine (169) at room temperature afforded a mono-N-oxide, whereas oxidation at 50° yielded an isomeric substance of higher melting point, which was shown by unambiguous synthesis¹²⁷ to be the 1-N-oxide (170). Because of its conversion by peracetic acid into the 1-N-oxide (170), the lower melting isomer was assumed to be the 2-N-oxide (171).



Our attempts to reproduce these results failed. The 1-N-oxide (170) was the sole product obtained by peracid oxidation of the benzo-1,2,4-triazine (169) at both temperatures as shown by identical i.r. spectra, mixed m.p. and a single spot on T.L.C..

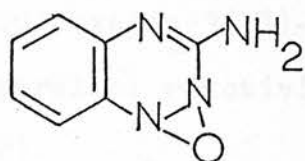
Benzo-1,2,4-triazine and benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) are resistant to nitration even under forcing conditions.¹²⁷ In contrast, 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a) is readily nitrated in high yield giving a compound whose structure was not formulated.¹²⁷ On the basis of the similar melting-point, Moed and his coworkers¹³⁴ suggested that the product of nitration is identical with 3-amino-7-nitrobenzo-1,2,4-triazine 1-N-oxide (172) whose structure they established by unambiguous synthesis.¹³⁴ This is, of course, the most likely product as the π -electron density at C(7) is high due to the combined mesomeric effects of the 3-amino group and the 1-N-oxide group. In our hands the product obtained on nitration of the N-oxide (161a) differed considerably in m.p. and solubility from that obtained previously,^{127,134} but its mass spectrum indicated that it had the correct molecular weight. The position of substitution was determined unequivocally by the splitting pattern of the ¹H n.m.r. spectrum, which is an ideal example of the spectrum of a 7-substituted benzo-1,2,4-triazine 1-N-oxide (see Figure 3). H(6) and H(8) were found at very low field because of the effect of the adjacent nitro group, H(8) being deshielded at the same time by the 1-N-oxide group.



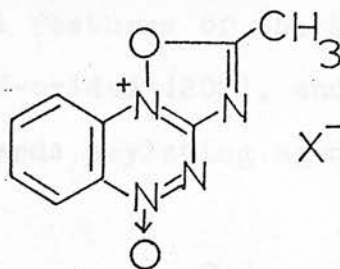
Attempted bromination of the 1-N-oxide (161a) under reaction conditions effective for o-nitroaniline, failed to produce a 7-bromo derivative.

The quaternary salts of heterocyclic N-oxides often show greater reactivity towards nucleophiles than the N-oxides themselves. In order to study this type of reactivity, an attempt was made to prepare a quaternary salt of 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a). This N-oxide (161a) however, showed no reactivity towards alkylation by methyl iodide.

In view of the current interest in the photochemical rearrangements of heterocyclic N-oxides^{108,109} (see Introduction, page 29) it was considered of interest to examine the stability of benzo-1,2,4-triazine N-oxides to u.v. irradiation. Since the 2-N-oxide (165a) is now known to exist (see above) it was considered that this compound might be obtained, via the intermediate oxadiaziridine (173), by photochemical rearrangement of the 1-N-oxide (161a). The 1-N-oxide (161a) was, however, unaffected by u.v. light from a medium pressure source.



(173)



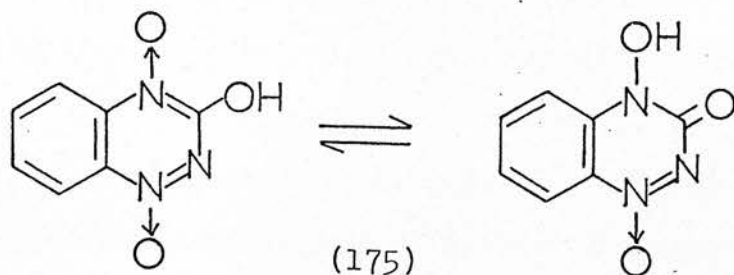
(174)

It is known that 2-acetylamino pyridine N-oxides, and related compounds, undergo a facile cyclisation on heating to give oxadiazolones⁶⁴ (see Introduction, page 28). It was thus of interest to see if the acetylamino compound (164a) would cyclise in a similar manner to afford the oxadiazolium salt (174). Treatment with concentrated sulphuric acid afforded a yellow solid which would not form a fluoroborate. This fact and the conversion of the yellow solid with water into the di-N-oxide (163a) suggests that the yellow solid was a sulphate. It is conceivable that, although the overall effect is merely hydrolysis of the acetylamino group, the hydrolysis may be aided by participation by the N-oxide group.

One of the reasons for preparing the di-N-oxide (163a) and for establishing its structure with certainty was its possible use as an intermediate for the synthesis of 4-hydroxybenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (175). It was of interest to see if this di-N-oxide (175) would behave in an analogous manner to the mono-N-oxide (176) which undergoes the novel ring contraction¹²⁶ to benzotriazole on treatment with alkali, mentioned previously. Also the di-N-oxide (175), which exists in the cyclic hydroxamic acid form,



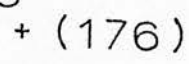
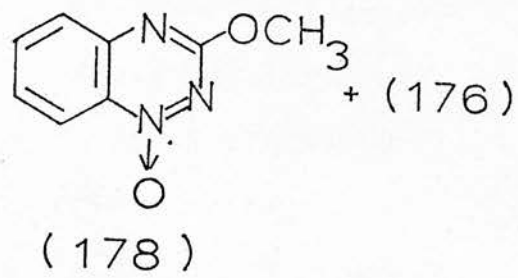
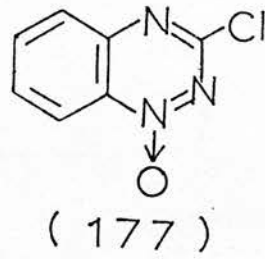
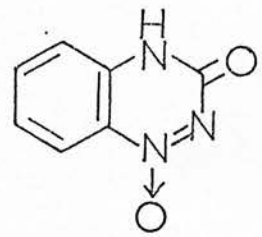
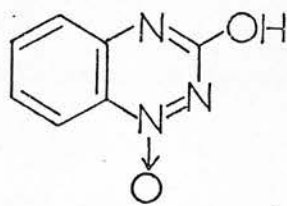
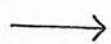
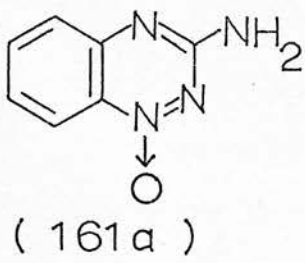
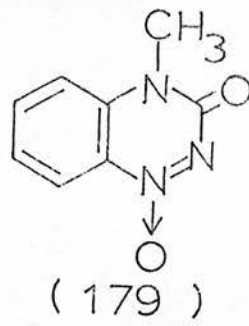
possesses many of the structural features of the 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxides (202), and could thus exhibit parallel reactivity towards acylating agents (see Section 2).



The first approach to the synthesis of 4-hydroxybenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (175) involved the attempted diazotisation of the 3-amino-1,4-di-N-oxide (163a). This resulted in recovery of unchanged starting material. This result was not altogether unexpected because of the known resistance of 2-aminoquinoxaline 1-N-oxides to diazotisation.¹³⁵ The 1-N-oxide (161a), however, does not possess this structural feature and is readily converted by diazotisation¹²³ into benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176).

Attempted peracid oxidation of the 1-N-oxide (176) under conditions which produced di-N-oxides from the 3-amino-1-N-oxides (161), was unsuccessful. Again, this result was not really unexpected because the basicity of the nitrogen atom, N(4), is greatly reduced by the fact that the 1-N-oxide (176) exists predominantly in the cyclic amide form.

Another possible synthetic approach, which is a standard procedure for other ring systems,¹³⁹ involves peracid oxidation of a compound possessing a substituent at C(3)



which can then be hydrolysed to give the required product. The presence of a suitable electron-releasing group at C(3) should also enhance the reactivity of N(4) to N-oxidation (see Introduction, page 5). The 1-N-oxide (176) is readily converted¹²³ into the corresponding 3-chloro derivative (177) using phosphorus oxychloride. Peracid oxidation of the 3-chloro-1-N-oxide (177) at 45 - 50° afforded unchanged starting material. Raising the temperature to 80° only resulted in the hydrolysis of the 3-chloro group giving benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176). On the assumption that the nitrogen atom, N(4), was still not sufficiently activated to promote N-oxidation, the peracid oxidation of the 3-methoxy-1-N-oxide (178) was next studied. This compound was prepared by the reaction of the 3-chloro-1-N-oxide (177) with hot methanolic sodium methoxide. Simultaneous hydrolysis gave rise to a small amount of benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176). The 3-methoxy-1-N-oxide (178) was recovered unchanged on attempted peracid oxidation at 45 - 50°. At 80° decomposition occurred and only a small amount of the benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) was isolated.

Despite the failure to synthesise 4-hydroxybenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (175) a model system was still available for the study of the potential reactivity of benzo-1,2,4-triazin-3(4H)-one N-oxides with acylating agents. 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179) is structurally similar to the 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxides (216), which react readily

with acylating agents (see Section 2). This N-methyl-1-N-oxide can be obtained by methylation of benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176),¹²³ and is completely different in its properties from the corresponding O-methyl derivative (178). An attempt at a direct, one-step synthesis of the N-oxide (179) from N-methyl-o-nitroaniline and cyanamide was unsuccessful, the basicity of the amine hydrogen atom being insufficient to form the intermediate guanidine required. Although benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) showed itself reactive towards nucleophilic substitution, the N-methyl derivative (179) did not react with acetic anhydride under the reaction conditions employed, whereas acetylation of the fused benzene ring might have been expected to occur.

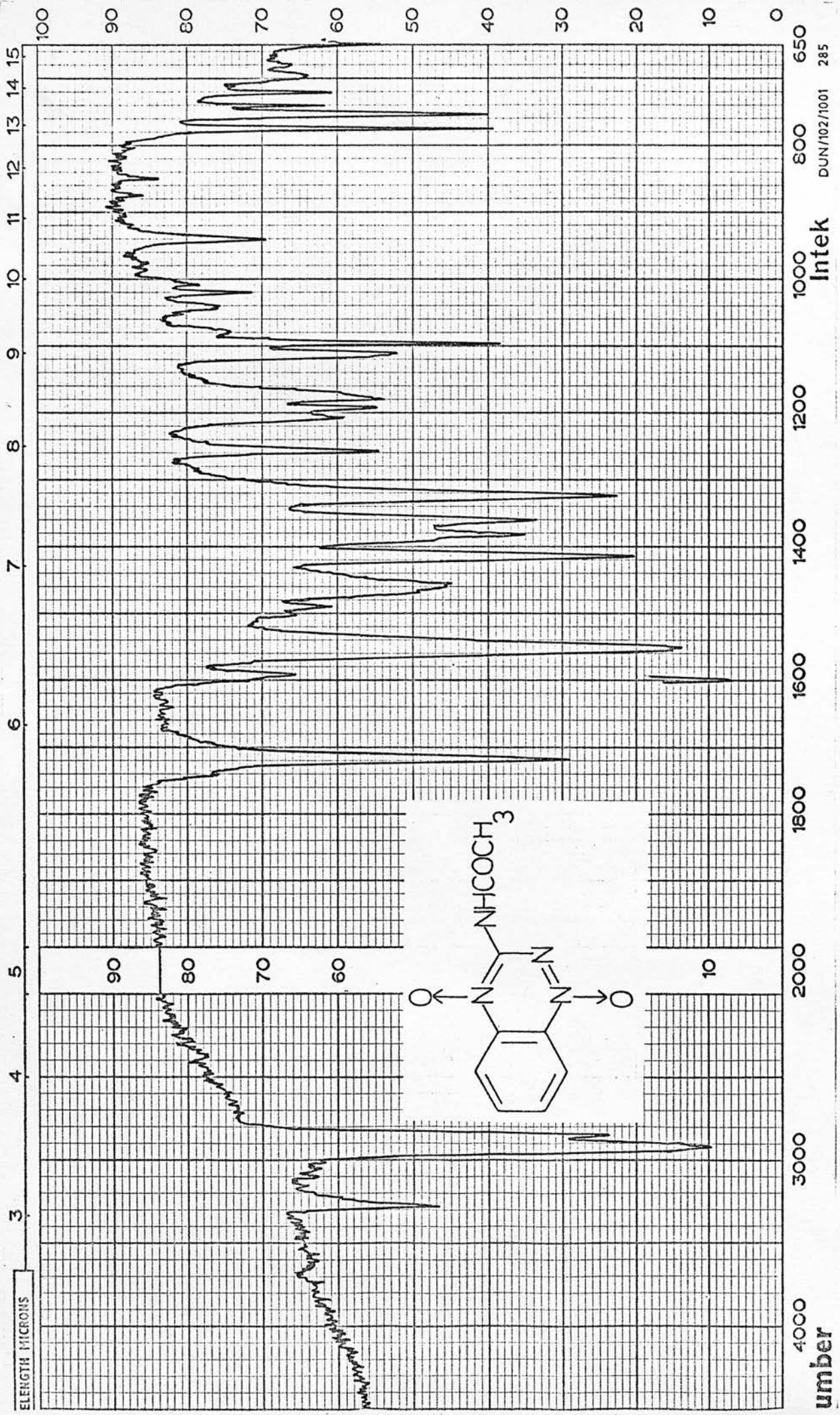


Figure 14 .

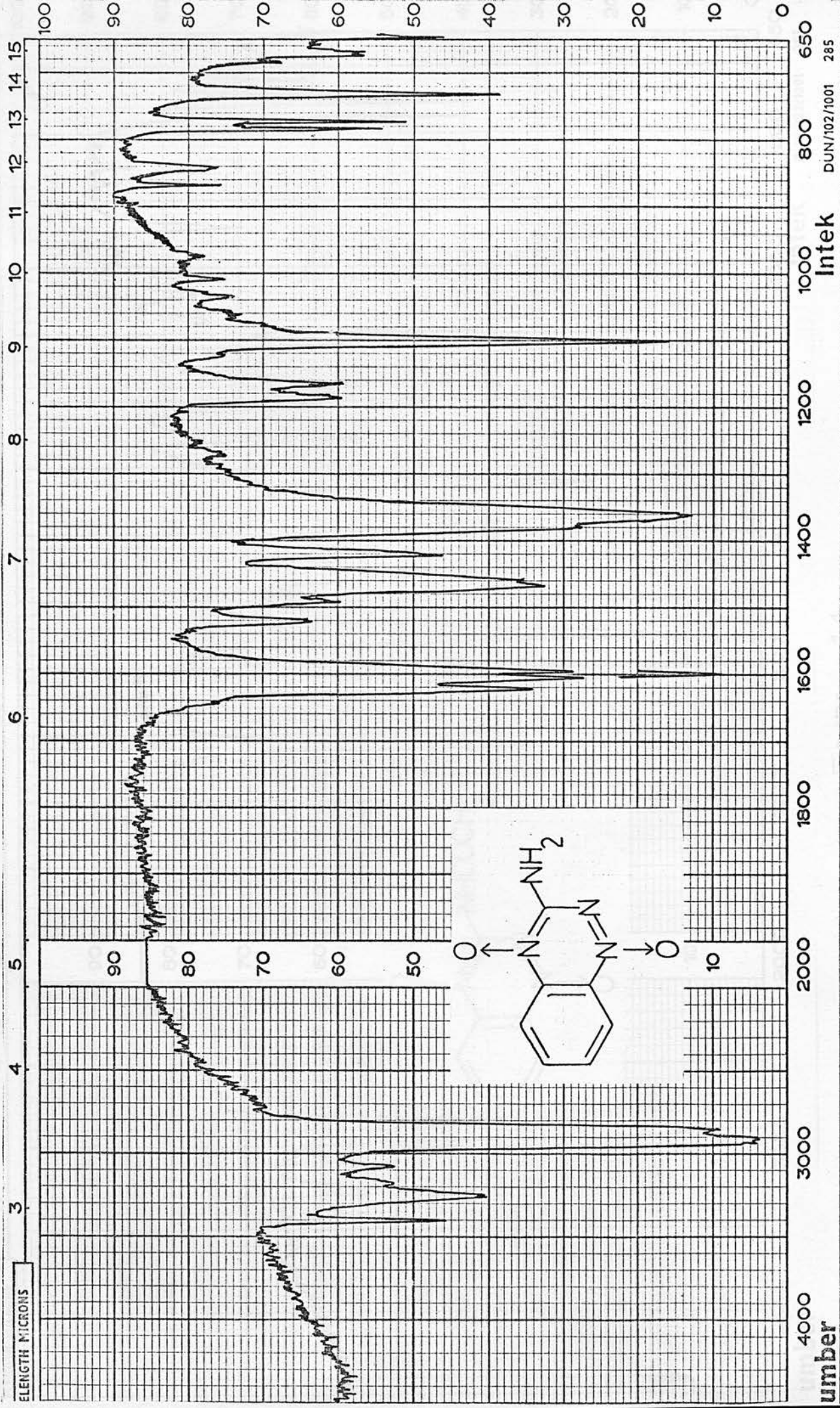


Figure 13

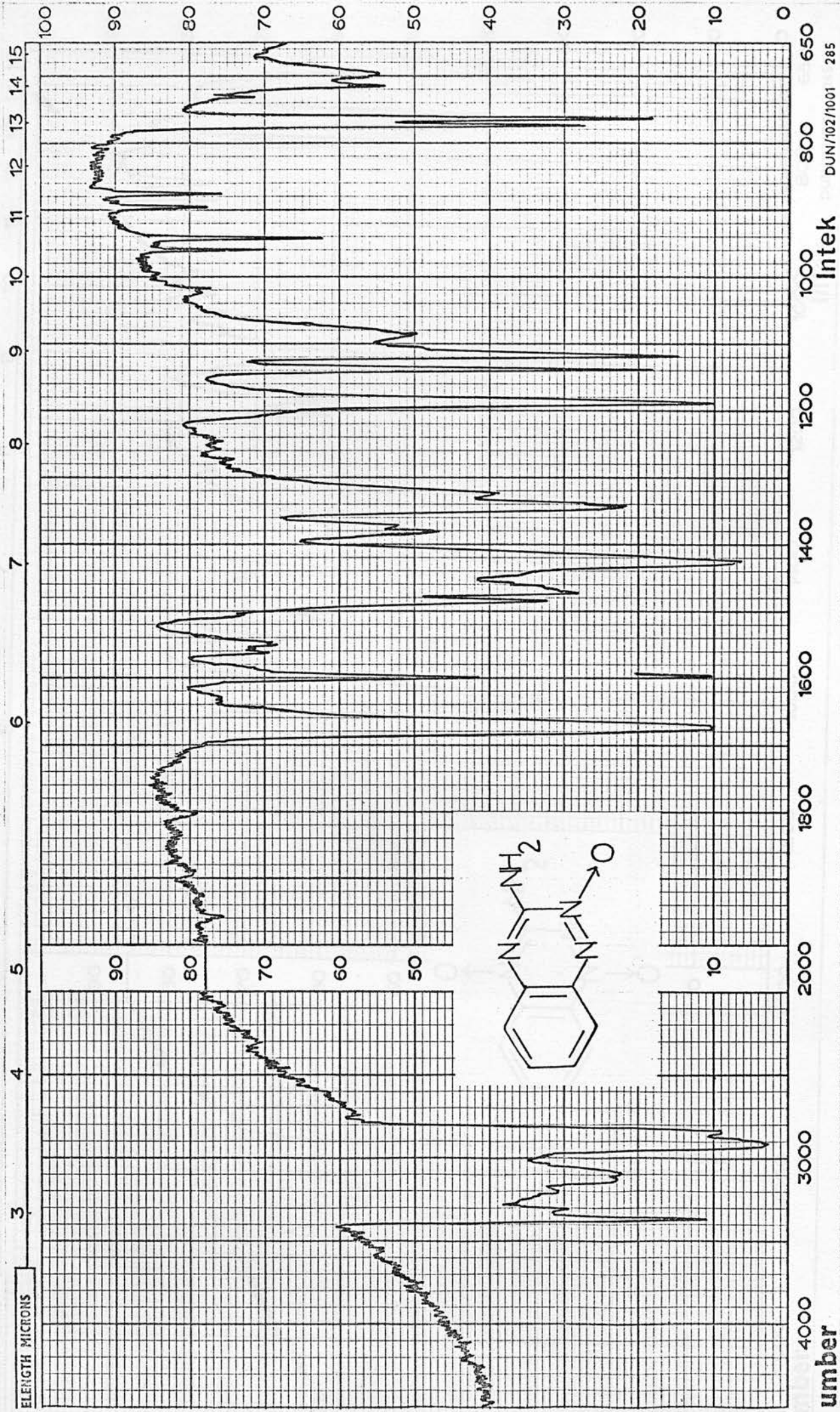


Figure 12.

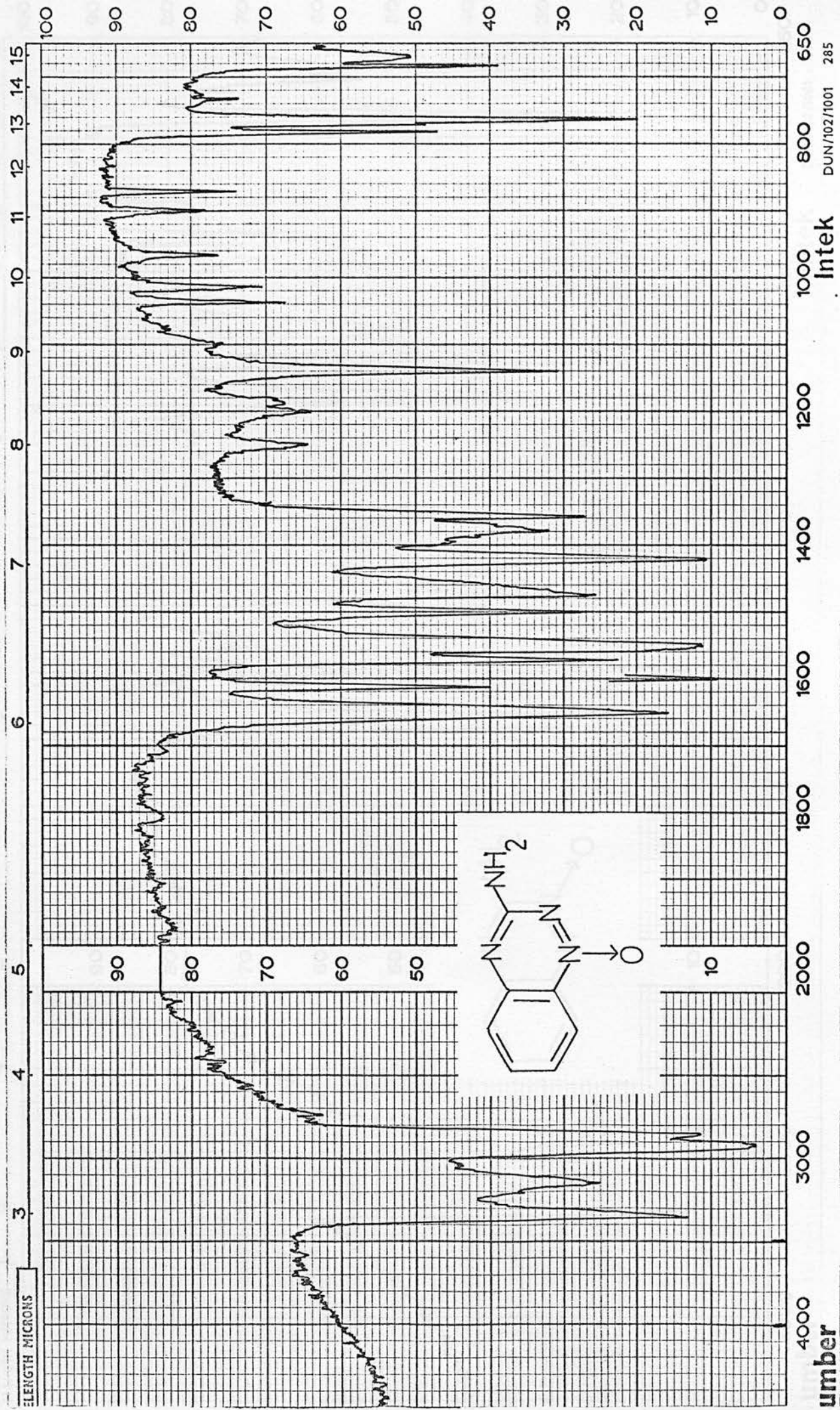


Figure 11.

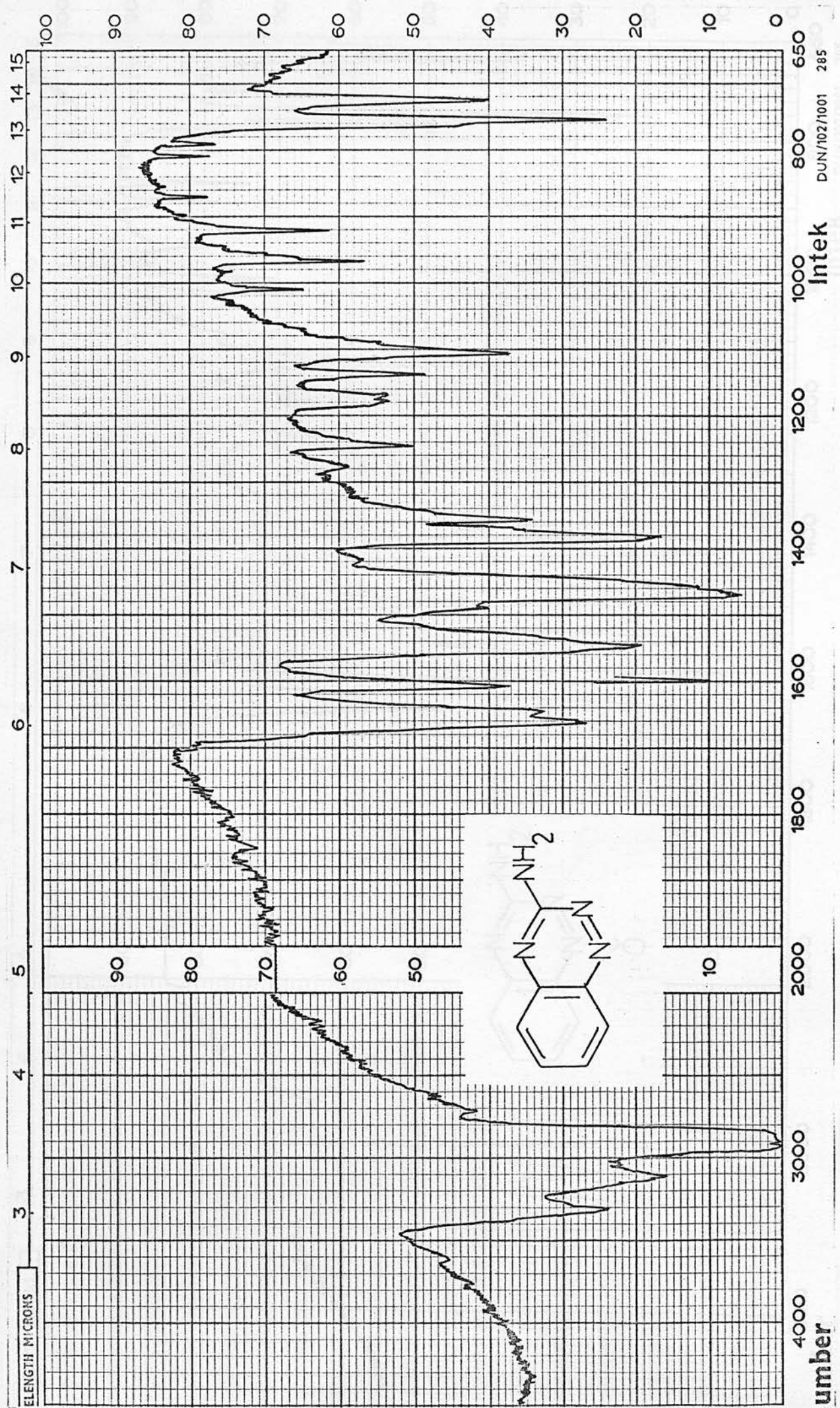
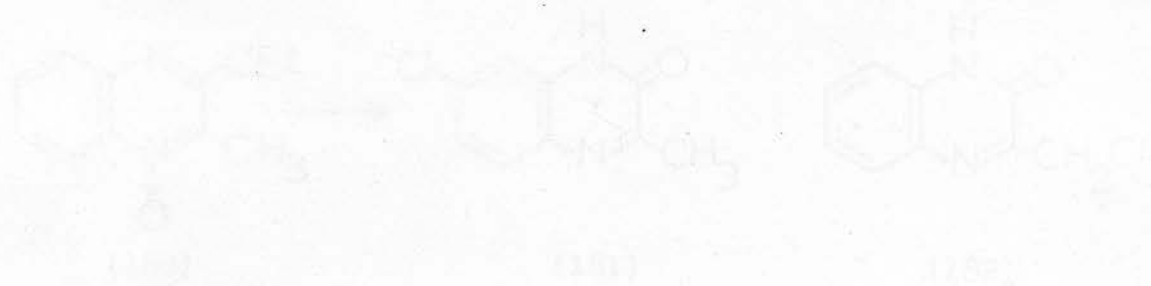


Figure 10.



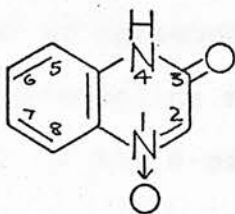
SECTION TWO

THE REACTIONS OF QUINOXALIN-3(4H)-ONE 1-N-OXIDES WITH ACYLATING AGENTS



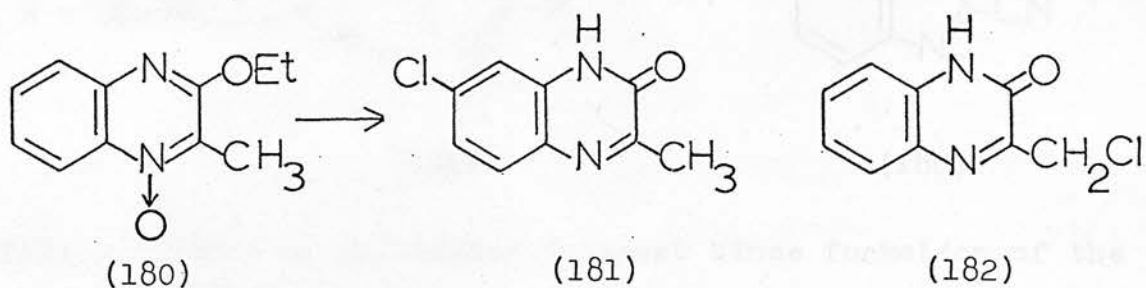
The acylation of quinoxalin-3(4H)-one 1-N-oxide (1) with acetic anhydride (2) was carried out in the presence of pyridine at room temperature. The reaction was complete after 24 hours. The product was purified by recrystallization from benzene and gave a white solid, mp 102-103°C. The mother liquor was evaporated and the residue was recrystallized from benzene, giving an additional crop of product. Total yield was 85%. The mother liquor was evaporated and the residue was recrystallized from benzene, giving an additional crop of product. Total yield was 85%.

THE REACTIONS OF QUINOXALIN-3(4H)-ONE 1-N-OXIDES WITH
ACYLATING AGENTS.



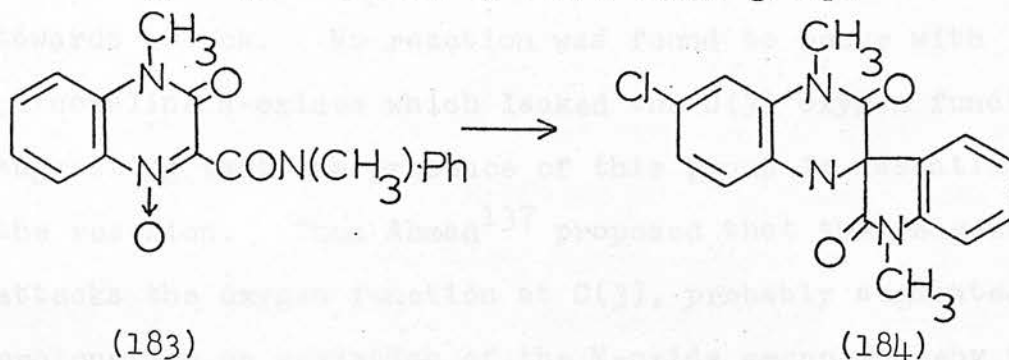
QUINOXALIN-3(4H)-ONE 1-N-OXIDE

Derivatives of quinoxalin-3(4H)-one 1-N-oxide possessing a phenyl substituent at C(2) exhibit unusual chemical reactivity. It has been shown recently^{137,138} that these compounds undergo chlorination at C(6) under such mild reaction conditions as heating with acetyl chloride or ethanolic hydrogen chloride. Earlier work by Newbold and Spring^{139,140} showed that 3-ethoxy-2-methylquinoxaline 1-N-oxide (180) on treatment with boiling ethanolic hydrogen chloride afforded 6-chloro-2-methylquinoxalin-3(4H)-one (181) rather than the expected 2-chloromethylquinoxalin-3(4H)-one (182).

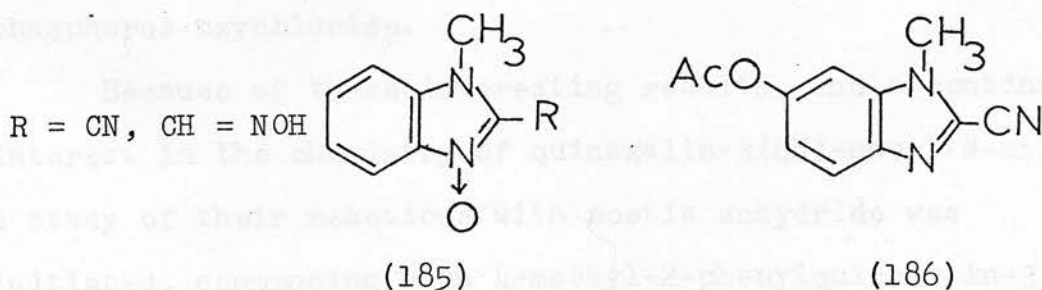


Similarly Clark-Lewis and Katekar¹⁴¹ confirmed the observation of Usherwood and Whitely¹⁴² that the reaction of the 4-methylquinoxalin-3(4H)-one 1-N-oxide derivative (183) with ethanolic hydrogen chloride also afforded a chlorine-containing product formulated¹⁴¹ as the spiro compound (184).

It was proposed¹⁴¹ that, by analogy with the Ingold re-arrangement¹⁴³ (phenylhydroxylamine \rightarrow p-chloroaniline) the product (184) was formed by nucleophilic attack on the benzene portion of the quinoxaline nucleus by chloride ion following on protonation of the N-oxide group.



Takahashi and Kano^{144,145} have observed similar behaviour in the reactions of certain benzimidazole N-oxides with nucleophiles. In particular, they report that reaction of the N-oxides (185) with acetic anhydride affords the acetoxy-derivative (186).



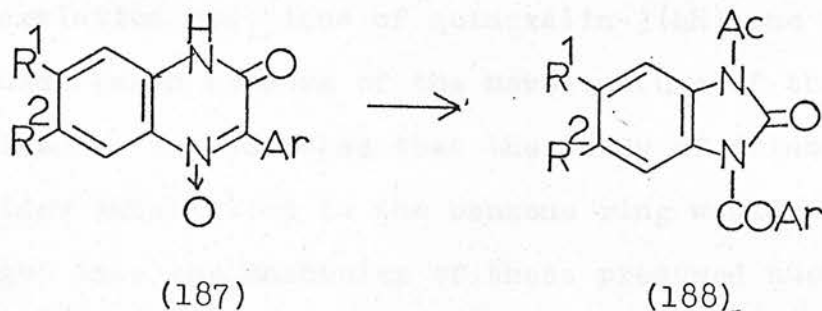
This result is of particular interest since formation of the acetoxy-derivative (186) implies nucleophilic attack by acetate ion which is normally a relatively poor nucleophile. Nucleophilic substitution of this type is rarely if ever observed and would provide a direct means of hydroxylating the aromatic nucleus of benzoheterocycles.

Ahmad and his co-workers have shown^{137,138} that the

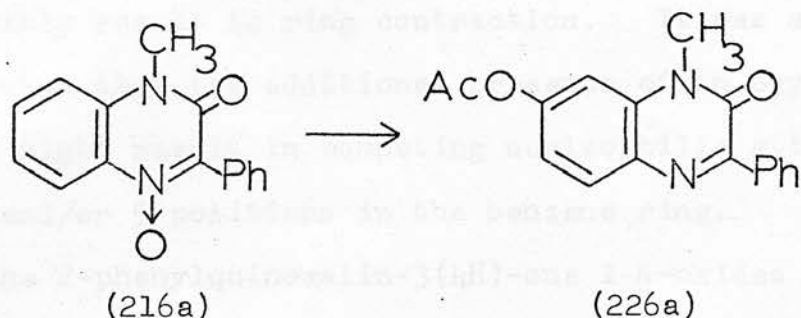
2-phenylquinoxalin-3(4H)-one 1-N-oxides (215) and (216) undergo chlorination at C(6). An interesting structural feature of these N-oxides (215) and (216) is that whereas substitution normally occurs at C(2) or at a methyl group, the phenyl group at C(2) effectively blocks this position towards attack. No reaction was found to occur with quinoxaline N-oxides which lacked the C(3) oxygen function, suggesting that the presence of this group is essential to the reaction. Thus Ahmad¹³⁷ proposed that the reagent attacks the oxygen function at C(3), probably augmented by protonation or acylation of the N-oxide group whereby C(6) becomes electron deficient and hence prone to attack by chloride ion (see Scheme 5, page 90). Cheeseman¹⁰⁶ has, however, reported that 2,3-diphenylquinoxaline 1-N-oxide and 1,4-di-N-oxide, which have no C(3) oxygen function, both undergo chlorination in the benzene ring when reacted with phosphorus oxychloride.

Because of these interesting results, and a continuing interest in the chemistry of quinoxalin-3(4H)-one 1-N-oxides,¹⁴⁶ a study of their reactions with acetic anhydride was initiated, commencing with 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a). During the early stages of this work Ahmad and his co-workers¹⁴⁷ published a paper describing the reactions of the N-oxide (216a) and other quinoxaline N-oxides with acetic anhydride. They showed that quinoxalin-3(4H)-one 1-N-oxides (187) bearing an aryl substituent at C(2), a carbonyl group at C(3), and a free hydrogen atom at N(4) are transformed by reaction with acetic

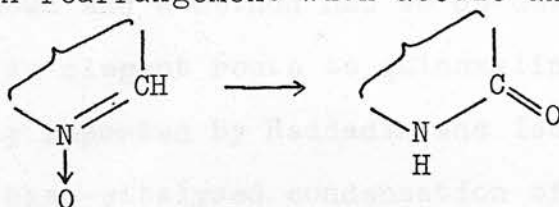
anhydride into 1-acetyl-3-acylbenzimidazolones (188).



On the other hand, if the free hydrogen at N(4) is replaced by a methyl group, the N-methyl-N-oxide (216a) undergoes a different type of reaction and an acetoxy group is introduced into the C(6) position of the benzene ring with simultaneous loss of the N-oxide group thereby affording the compound (226a).

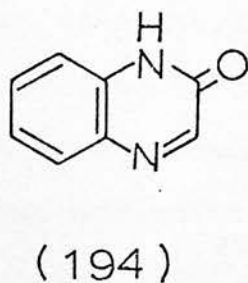
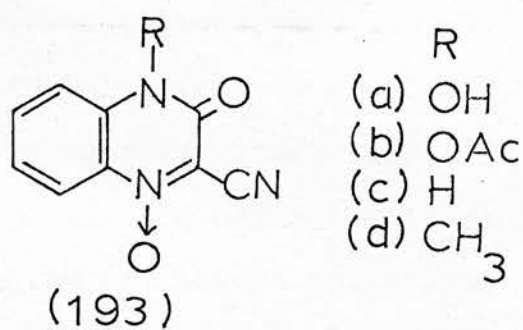
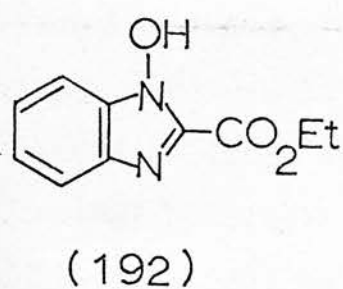
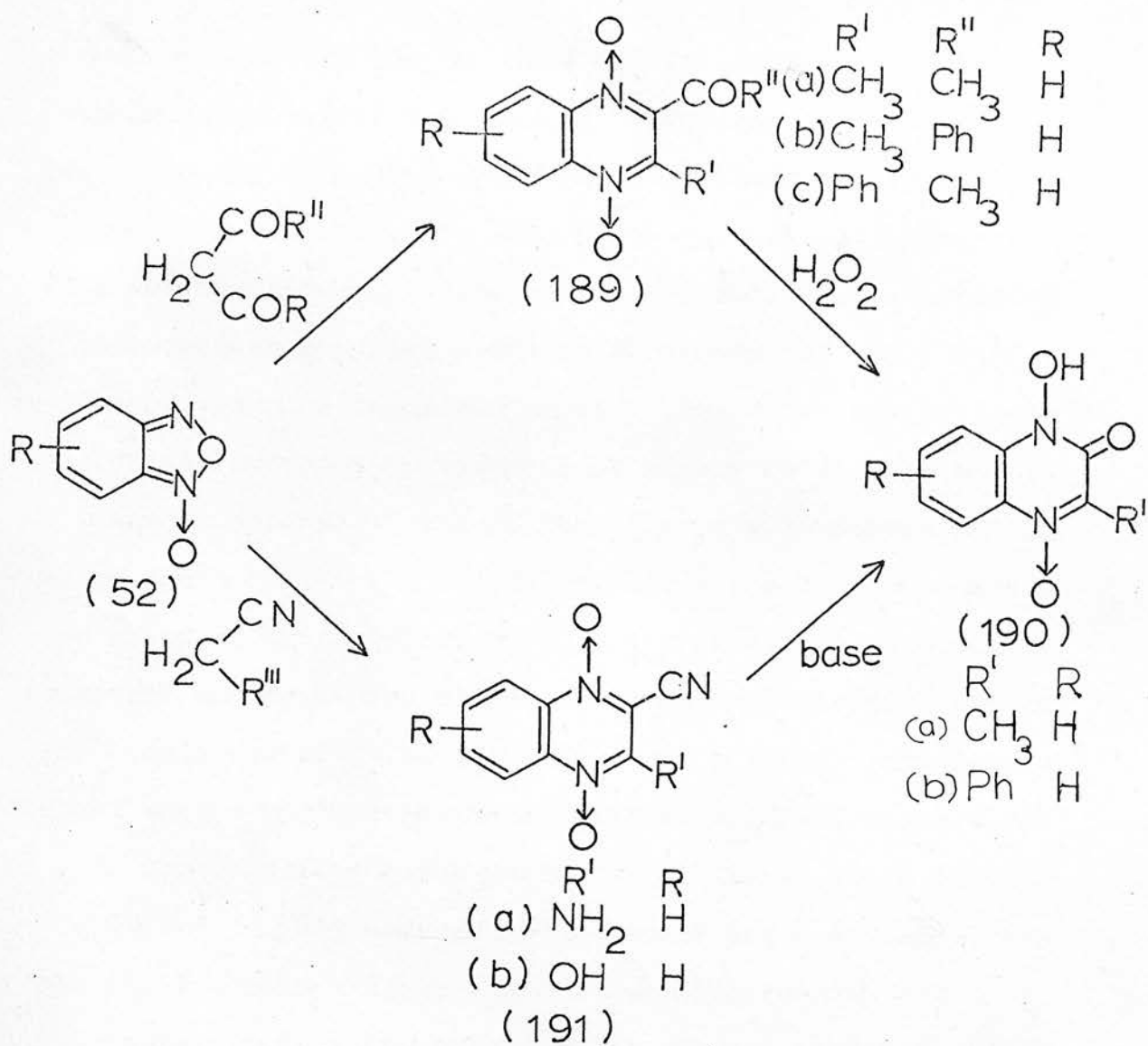


Our results from this reaction were in accord with Ahmad's findings. As previously found in the reactions with acetyl chloride,¹³⁷ quinoxaline derivatives lacking the C(3) oxygen function failed to react with acetic anhydride.¹⁴⁷ Quinoxaline N-oxides, unsubstituted at C(2) gave the expected and well-known rearrangement with acetic anhydride -



A closer study of the scope of the halogenation and acetoxylation reactions of quinoxalin-3(4H)-one 1-N-oxides was undertaken because of the novel nature of the processes involved. It was hoped that the study of quinoxaline N-oxides substituted in the benzene ring would provide some insight into the mechanism of these presumed nucleophilic substitution reactions. Thus, nucleophilic substitution at the 6-position should be promoted or retarded depending on the nature of a substituent in the 7-position. Also, the presence of a substituent at the 6-position might be expected to divert attack to the 8-position (which would be strong evidence for the nucleophilic nature of the reaction) or possibly result in ring contraction. It was also anticipated that the additional presence of an oxygen function at N(4) might result in competing nucleophilic attack at the 7- and/or 5-positions in the benzene ring.

The 2-phenylquinoxalin-3(4H)-one 1-N-oxides (215) and (216), required for the halogenation and acetoxylation studies were readily available by a known synthetic route^{148,149} involving the base-catalysed cyclisation of 2-nitro- α -phenyl-acetanilides (214), and methylation of the N-oxides thus obtained. The corresponding quinoxalin-3(4H)-one 1-N-oxides possessing an additional oxygen function at N(4) were, however, unknown and a method had to be devised for their synthesis. An elegant route to quinoxaline 1,4-di-N-oxides (189) recently reported by Haddadin and Issidorides,¹⁵⁰ involves the base-catalysed condensation of benzofuroxan (52; R=H) with active methylene compounds. This method was



chosen as the synthetic route to 4-N-oxygenated substrates required for the studies mentioned above. While this synthetic approach was being studied, details appeared of a comprehensive survey of the condensations of benzofuroxans with a variety of active methylene compounds.¹⁵¹ The 4-N-oxygenated compounds, analogous to the N-oxides (215) and (216) are of the type (190), and it was thought that treatment of the 1,4-di-N-oxides (189) with hydrogen peroxide would cause the acyl group to be replaced by a hydroxyl group thus yielding the desired products (190).¹³⁵ An alternative approach involved the base-catalysed displacement of the cyano-group¹⁵² in the di-N-oxides (191) to afford the cyclic hydroxamic acids (190).

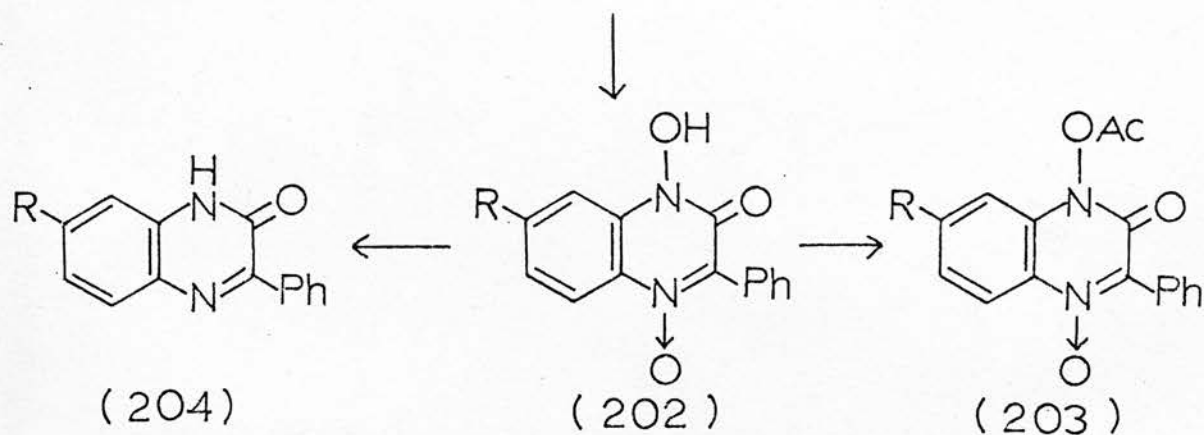
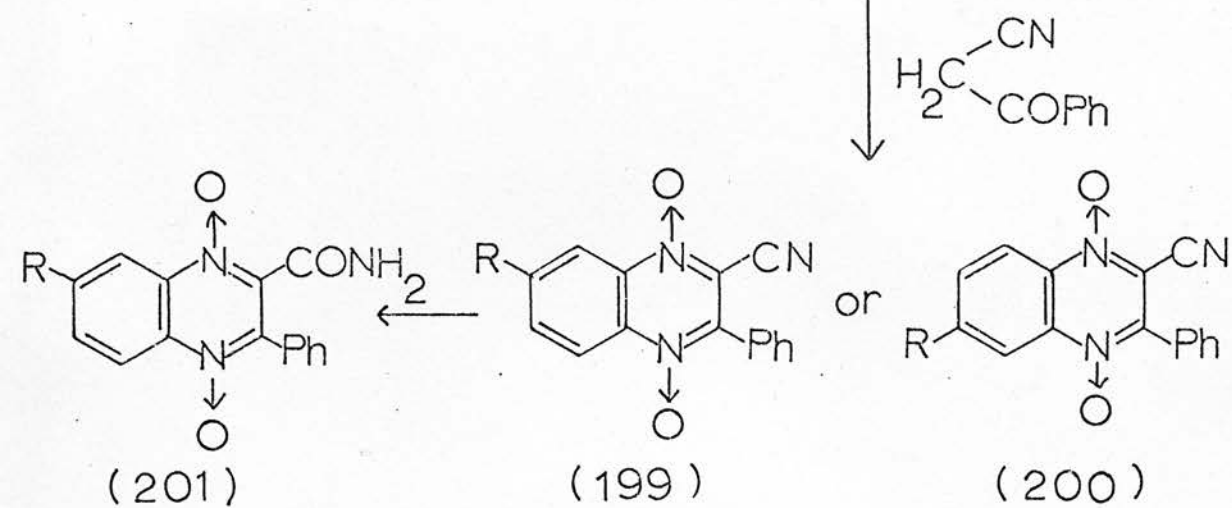
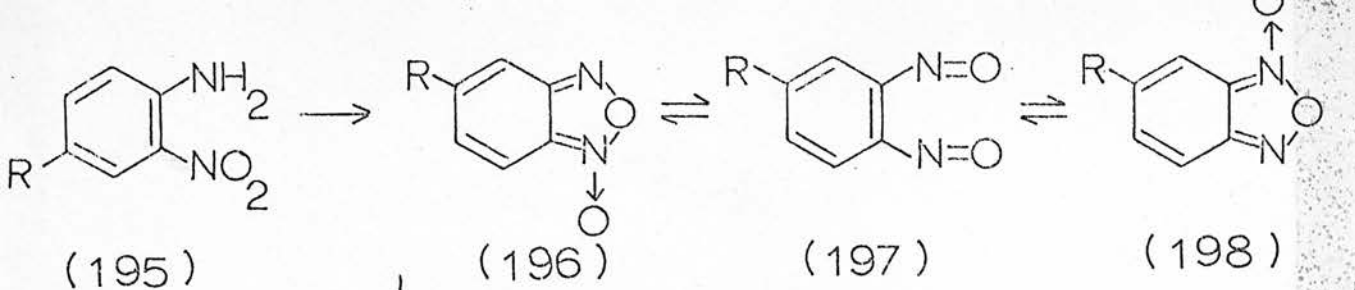
Benzofuroxan (52; R=H) condensed readily with acetylacetone in the presence of triethylamine as previously described,¹⁵⁰ or in ethanol-piperidine to afford 2-acetyl-3-methylquinoxaline 1,4-di-N-oxide (189a). Attempts to react benzofuroxan (52; R=H) with acetylacetone using different catalysts were not successful. The use of ethereal hydrogen chloride or a sodium bicarbonate-acetic anhydride mixture resulted in the recovery of starting material. The attempted use of sodium methoxide as a basic catalyst resulted in the formation of a dark (possibly polymeric) substance which was not characterised. The use of ethanol-piperidine as reaction medium was also suitable for the condensation of benzofuroxan (52; R=H) with benzoylacetone. This reaction can, in theory, give two condensation products (189b) and/or (189c). In practice a single product was obtained. The

absence of an isomer in the crude product was demonstrated by a single spot on T.L.C., sharpness of melting point, and a relatively simple ^1H n.m.r. spectrum, uncomplicated by extra signals indicative of a mixture. The condensation product is formulated as the benzoyl-di-N-oxide (189b) rather than the acetyl compound (189c). The assigned structure (189b) is based on the lower stretching frequency (ν_{max} , 1680 cm^{-1}) of the carbonyl group compared with that in the compound (189a). The orientation (189b) is also in accord with the greater reactivity of acetyl groups compared with benzoyl groups in aldol-type condensations. Attempts to convert the di-N-oxide (189a) into the corresponding cyclic hydroxamic acid (190a) using peracetic acid at room temperature or under reflux were unsuccessful. This hydroxamic acid (190a) has very recently been synthesised¹⁵³ by direct reaction of o-benzoquinone dioxime with methyl glyoxal.

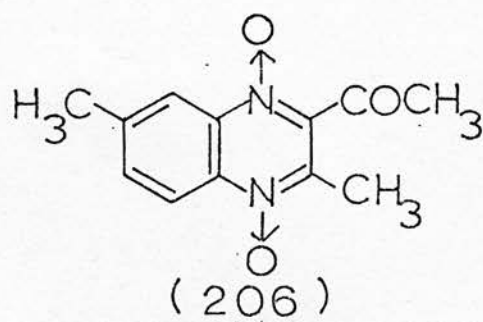
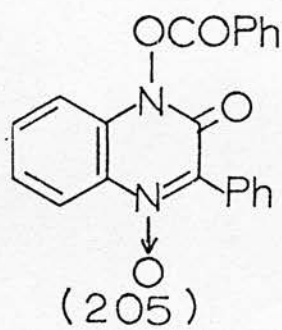
In view of the failure of the acetyl di-N-oxide (189a) to afford the cyclic hydroxamic acid (190a) on treatment with hydrogen peroxide, attention was turned to the application of Haddadin's synthesis to the preparation of cyano-di-N-oxides suitable for the nucleophilic displacement mentioned above. As reported by Ley et al.¹⁵¹ condensation of benzofuroxan (52; R=H) and malononitrile in ethanol-piperidine afforded the amino nitrile (191a). Reaction of benzofuroxan (52; R=H) with ethyl cyanoacetate in ethanol-piperidine afforded only a very small amount of red solid. This was assumed to be the piperidine salt of (191b) since its i.r. spectrum was similar to that of the red ammonium salt of (191b) which was

obtained by condensing ethyl cyanoacetate with benzofuroxan (52; R=H) in ethanolic ammonia. Acidification of the aqueous solution of this ammonium salt precipitated out a by-product, $C_9H_7N_3O_4$, which was not characterised. It may be relevant to point out that the N-hydroxybenzimidazole (192) is reported¹⁵⁴ to be a condensation product of benzofuroxan (52; R=H) with ethyl acetoacetate. Work up of the aqueous mother liquors afforded a yellow solid. The molecular weight and elemental analysis corresponded to the molecular formula $C_9H_5N_3O_3$ and the i.r. spectrum contained broad absorption at 3400 cm^{-1} . A deep red colour¹⁵² was obtained by treating this yellow solid with iron (III) chloride in ethanol, and warming with acetic anhydride afforded an acetoxy-derivative (193b) with a characteristic¹⁴⁸ i.r. absorption at 1800 cm^{-1} (cyclic:N.OAc). These properties are in accord with the cyclic tautomeric hydroxamic acid structure (191b) \rightleftharpoons (193a). In an attempt to verify this structure catalytic hydrogenation of the N-acetoxy derivative was carried out, the intention being to demonstrate the presence of a 2-cyanoquinoxalin-3(4H)-one nucleus in the molecule. However catalytic hydrogenation resulted in three equivalents of hydrogen being taken up to give the unsubstituted quinoxalin-3(4H)-one (194). This result is not unexpected since dithionite reduction of 2-cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) is known to afford quinoxalin-3(4H)-one (194).¹⁴⁸

In view of the ready condensation of ethyl cyanoacetate and malononitrile with benzofuroxan (52; R=H) it was anticipated that benzoylacetoneitrile would condense in a



- R
 (a) H
 (b) CH₃
 (c) OCH₃
 (d) Br
 (e) Cl



similar fashion to give the cyano di-N-oxide (199a) which on treatment with base should afford the N(4)-oxygenated analogue of the 2-phenylquinoxalin-3(4H)-one 1-N-oxides (215a) and (216a).

The condensation of benzoylacetone nitrile with benzofuroxan (52; R=H) occurred readily in triethylamine, or in ethanol or dimethylformamide in the presence of piperidine to afford in all three cases the expected 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a). However, though there was no increase in yield it was found more convenient to carry out the condensation in ethanolic ammonia at room temperature. The structure (199a) for the condensation product was fully in accord with its elemental analysis and molecular weight. The absence of i.r. absorption due to a cyano-group in this compound is not significant since it is not uncommon for cyano absorption to be very weak. The ^1H n.m.r. spectrum (Table 4) of this compound had a triple doublet at low field which integrated for two protons, demonstrating the presence of an N-oxide group on both N(1) and N(4). The nitrile proved to be stable to heating with 20% (w/v) aqueous sulphuric acid but in accord with its structure, warm ethanolic sodium ethoxide converted it, in high yield, with loss of the cyano group, into the cyclic hydroxamic acid (202a). This method proved to be very efficient as the hydroxamic acid product (202a) was formed as its sodium salt which was readily separated from any unreacted nitrile (199a). The cyclic hydroxamic acid (202a) was also formed when the nitrile (199a) was heated with 10% aqueous sodium hydroxide,

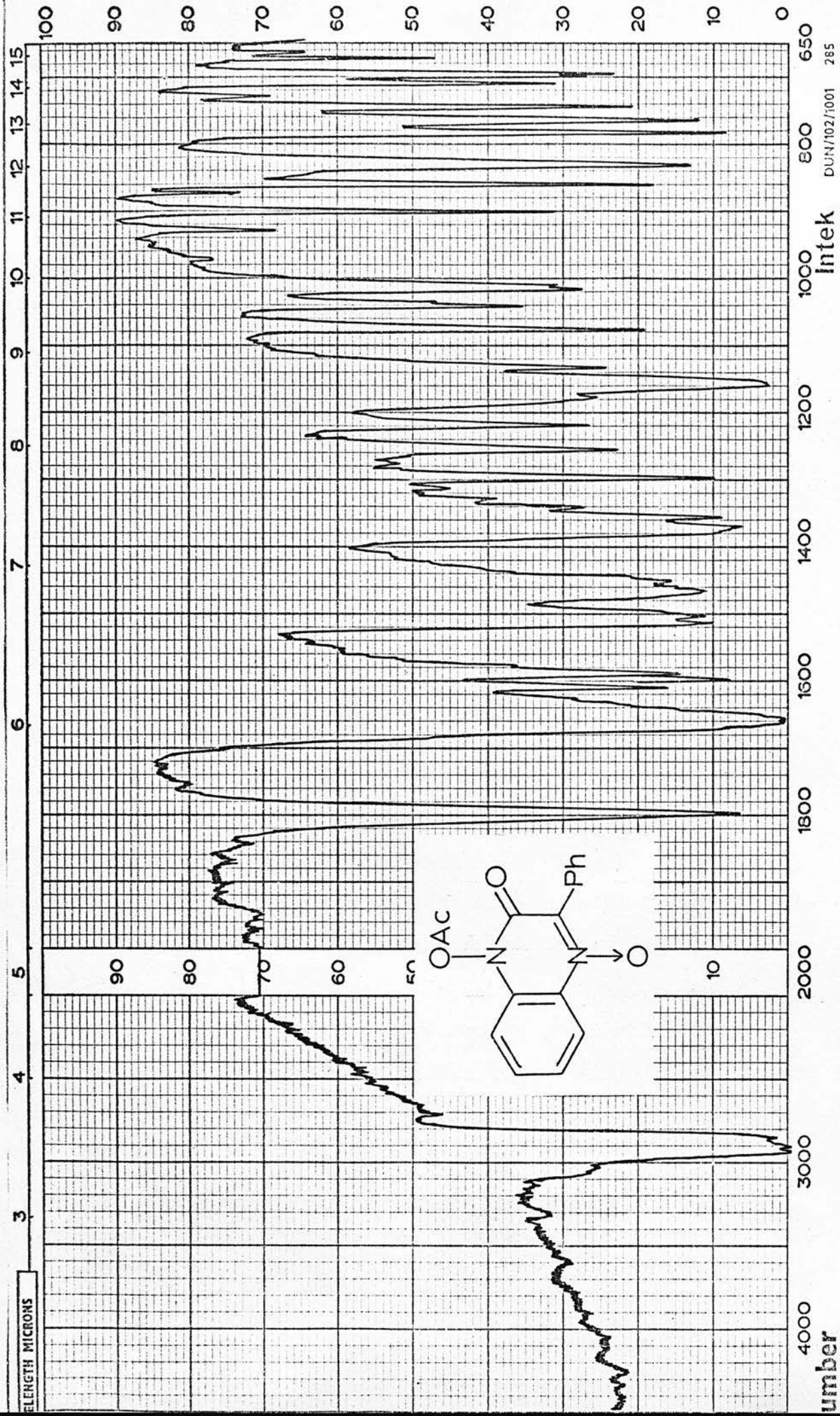


Figure 15.

but simultaneous hydrolysis of the cyano group occurred to give the amide (201a), and these two products were more difficult to separate. The structure (202a) for the cyclic hydroxamic acid is in accord with its elemental analysis and molecular weight and was confirmed by the deep red colour¹⁵² which it gave with iron (III) chloride in ethanol and by the formation of an acetoxy-derivative (203a) with a characteristic i.r. band at 1800 cm^{-1} (cyclic: N·OAc) (Figure 15). The cyclic hydroxamic acid (202a) also formed a benzoyl-derivative (205). The gross structure of the cyclic hydroxamic acid (202a) was established by reduction with sodium dithionite to 2-phenylquinoxalin-3(4H)-one (204a), identical with an authentic sample.

Although the cyano-group in 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) proved to be readily replaceable by ethoxide or hydroxide ion, it was unreactive towards nucleophiles such as aniline or ethyl cyanoacetate.

On prolonged heating of the cyclic hydroxamic acid (202a) with acetic anhydride, a product was obtained which analysed for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_5$. This product had strong carbonyl bands in the i.r. spectrum at 1790 and 1740 cm^{-1} (Figure 16) not present in the original molecule. The ^1H n.m.r. spectrum (Table 6) showed the presence of peaks at τ 7.50 and τ 7.67, integrating for three protons each. All of this evidence indicates the introduction of an N-acetoxy and a C-acetoxy group with loss of the N-oxide group. By analogy with the reaction of the N-methyl-N-oxide (216a) with acetic anhydride, the compound (221a), possessing an acetoxy-group

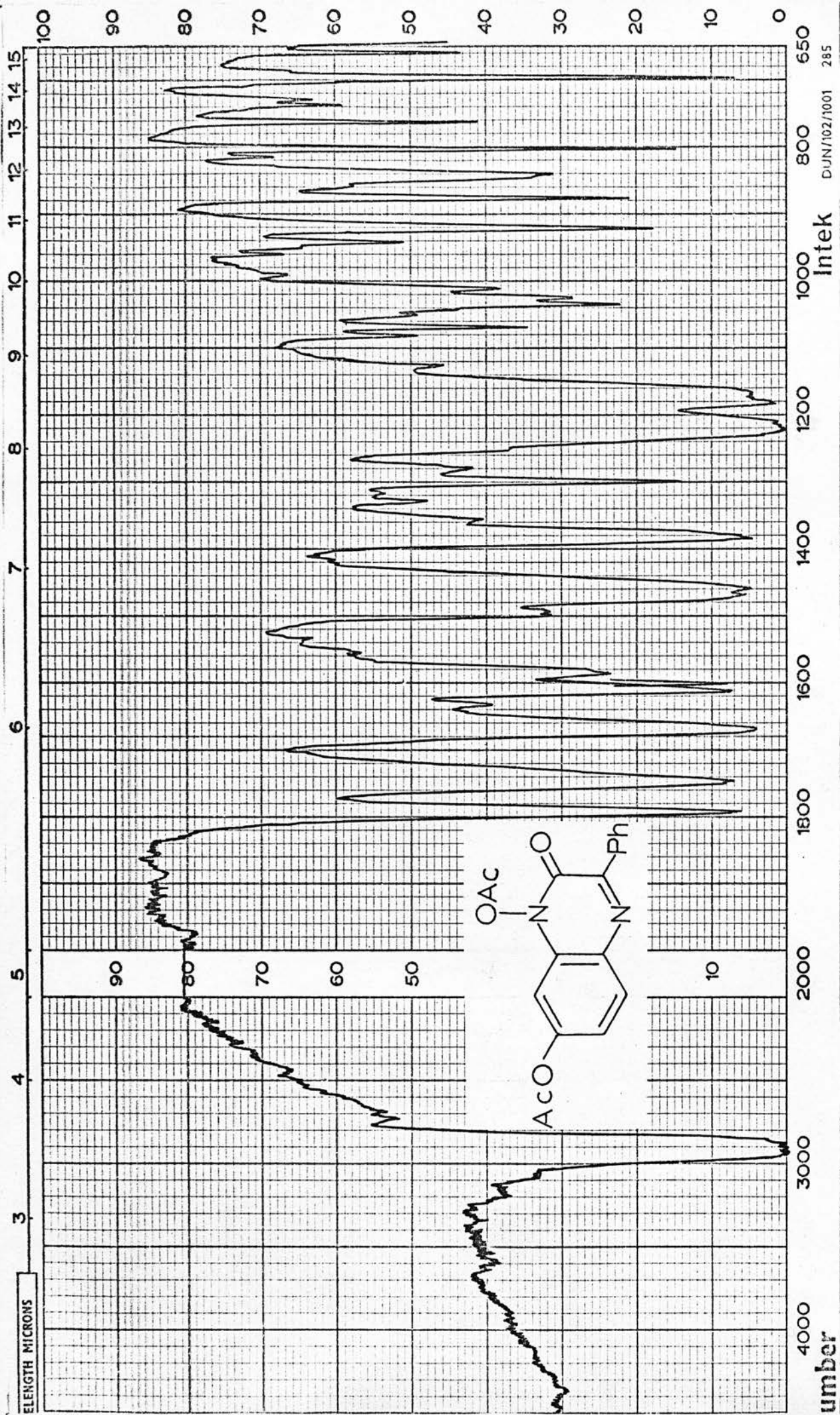
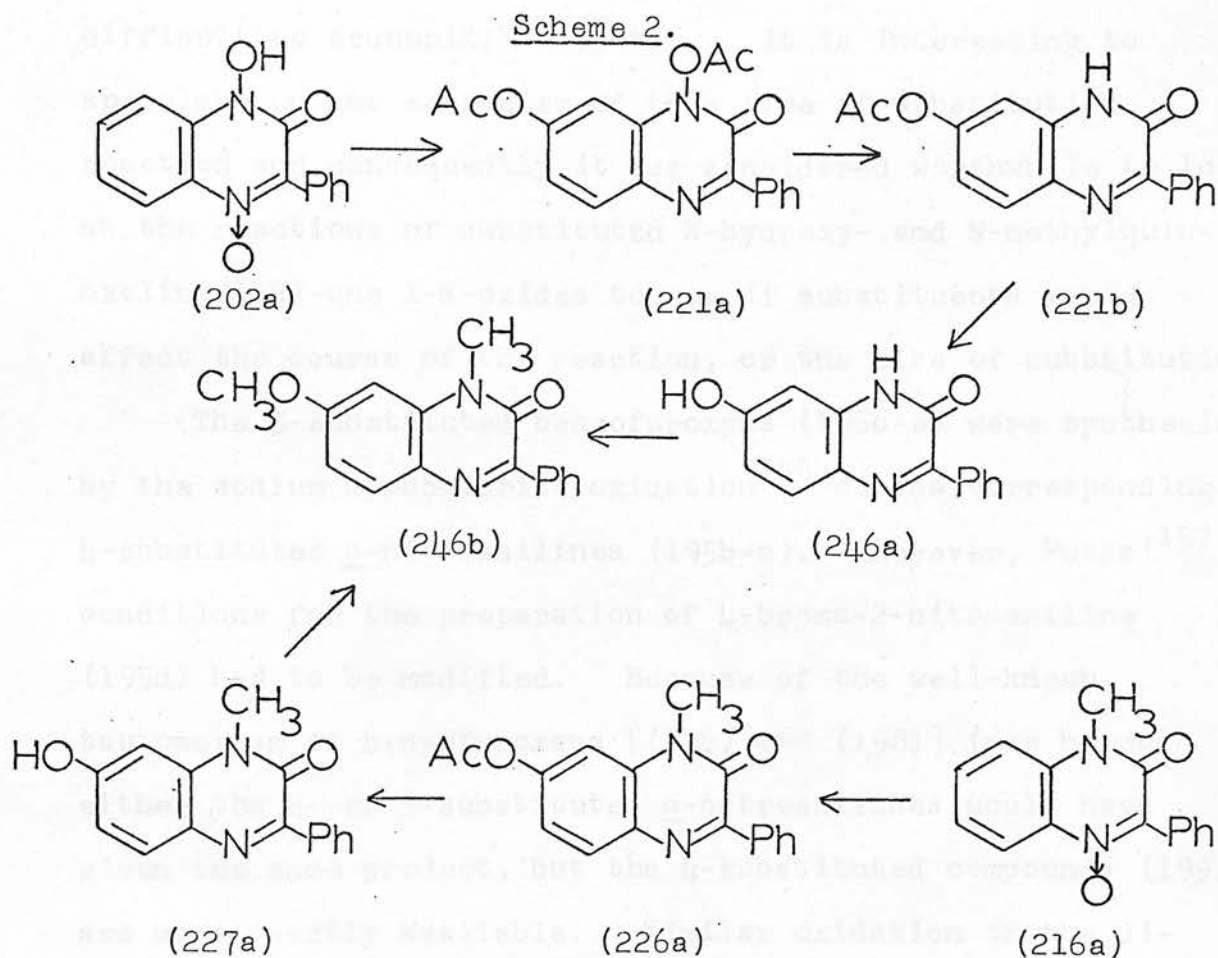


Figure 16.

at the C(6)-position was a possible structure for the diacetoxy-product. This hypothesis was proved to be correct by converting the diacetoxy compound into a quinoxalone whose structure was established by unambiguous synthesis (Scheme 2).



Catalytic hydrogenation of the diacetoxy-product caused hydrogenolysis of the N-acetoxy group giving compound (221b) which lacked the i.r. band at 1790 cm^{-1} , and the ^1H n.m.r. signal at $\tau\ 7.67$. Hydrolysis of the C-acetoxy derivative (221b) followed by methylation gave the quinoxalone (246b), prepared by Ahmad¹⁴⁷ from the N-oxide (216a) as indicated above in Scheme 2.

Formation of the diacetoxy-product (221a) from the

hydroxamic acid (202a) is one of the very few examples^{145,147,155} known in which an acetoxy-group is directly introduced into a benzene ring. Potentially it is a useful method for the hydroxylation of benzoheterocycles, a process normally difficult to accomplish directly. It is interesting to speculate on the mechanism of this type of substitution reaction and consequently it was considered worthwhile to look at the reactions of substituted N-hydroxy- and N-methylquinoxalin-3(4H)-one 1-N-oxides to see if substituents would affect the course of the reaction, or the site of substitution.

The 5-substituted benzofuroxans (196b-e) were synthesised by the sodium hypochlorite oxidation¹⁵⁶ of the corresponding 4-substituted o-nitroanilines (195b-e). However, Fuchs¹⁵⁷ conditions for the preparation of 4-bromo-2-nitroaniline (195d) had to be modified. Because of the well-known tautomerism of benzofuroxans [(196) \rightleftharpoons (198)] (see below) either the 4- or 5-substituted o-nitroanilines would have given the same product, but the 4-substituted compounds (195) are more readily available. Similar oxidation of the di-substituted o-nitroanilines (207) afforded the 5,6-disubstituted benzofuroxans (208).

The mechanism of the reaction of benzofuroxans with active methylene compounds has not been elucidated but it might be expected that with unsymmetrical reagents, isomeric quinoxaline derivatives would be obtained. It has been shown by Katritzky et al.^{158,159} that tautomerism in substituted benzofuroxans is rather facile, ¹H n.m.r. evidence indicating that for electron-withdrawing substituents, the

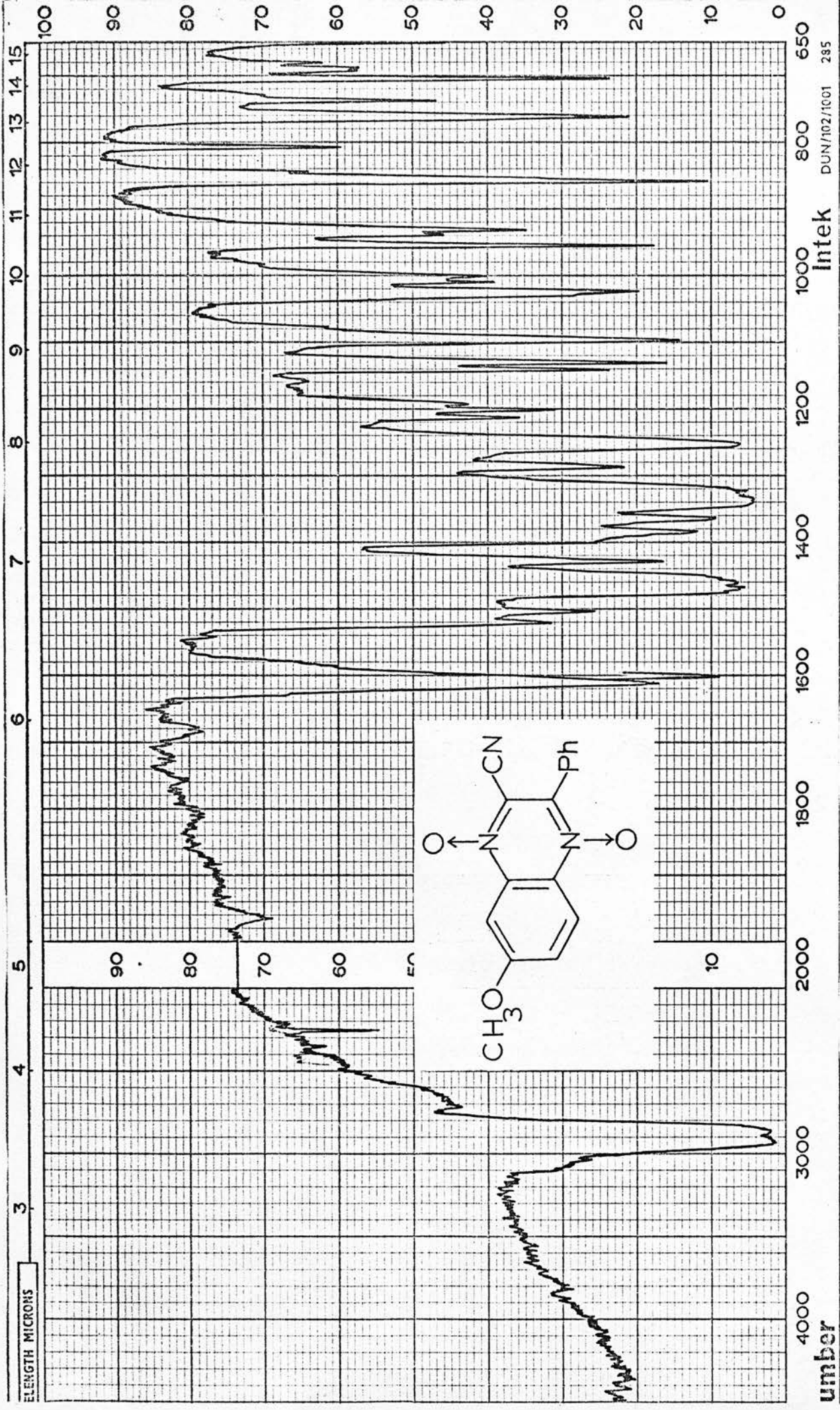
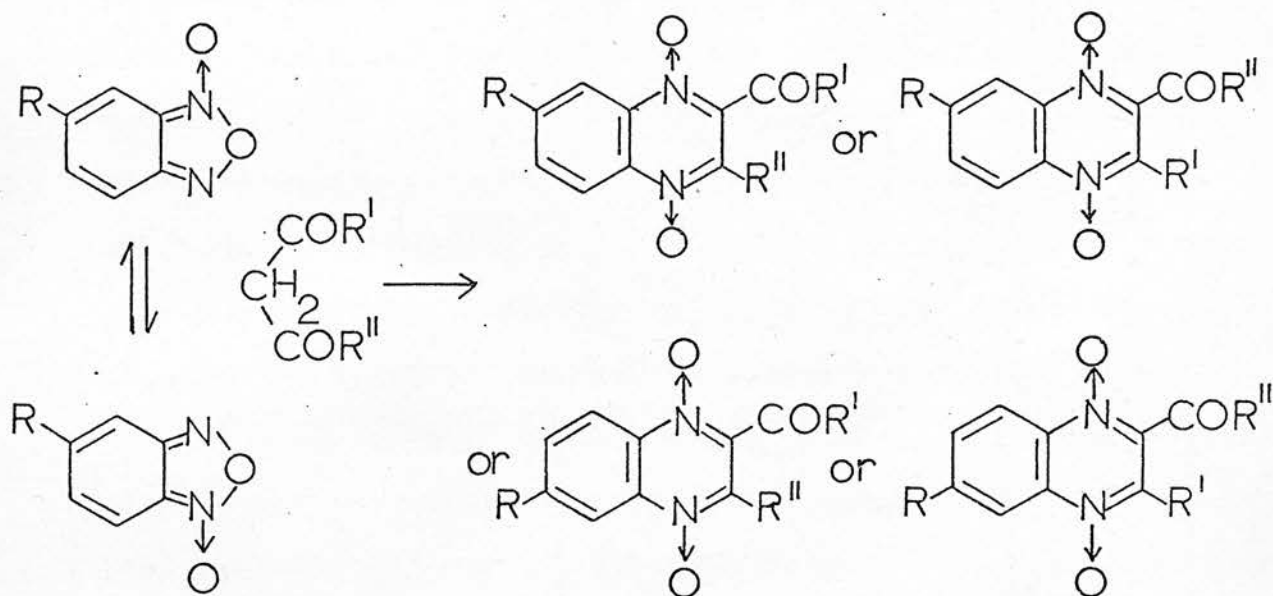


Figure 17.

stable tautomer is (198), whereas for electron-donating substituents, the tautomer (196) is favoured. It is clear that substituted benzofuroxans could react in either of the tautomeric forms (196) or (198) or as the intermediate dinitroso structure (197). Thus the reaction of substituted benzofuroxans with unsymmetrical dicarbonyl compounds could afford four different isomeric products, as shown in Scheme 3.

Scheme 3



However, in the case under study, the cyano group in the active methylene compound has been shown to be retained in the condensation product and thus there is a maximum of only two possible isomers. Assuming that the benzofuroxan reacts by a single pathway, two products should result if both tautomers are involved and only one product if a single tautomer is involved. The second factor to be considered is the mode of attack by the enolate anion of the methylene

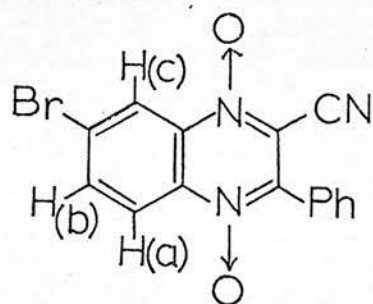
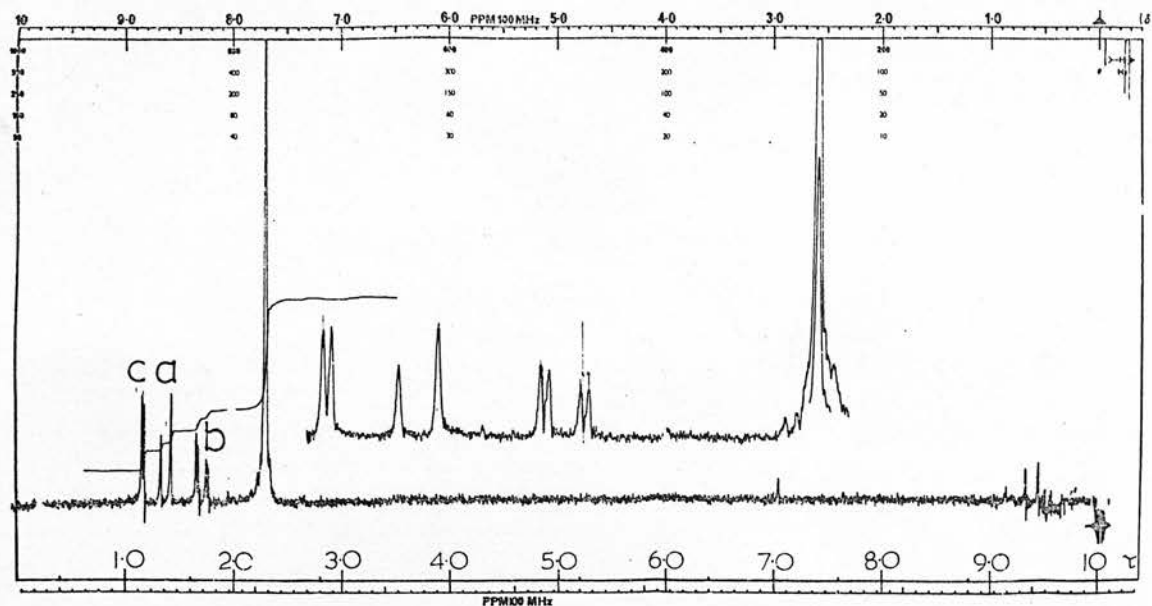


Figure 18.

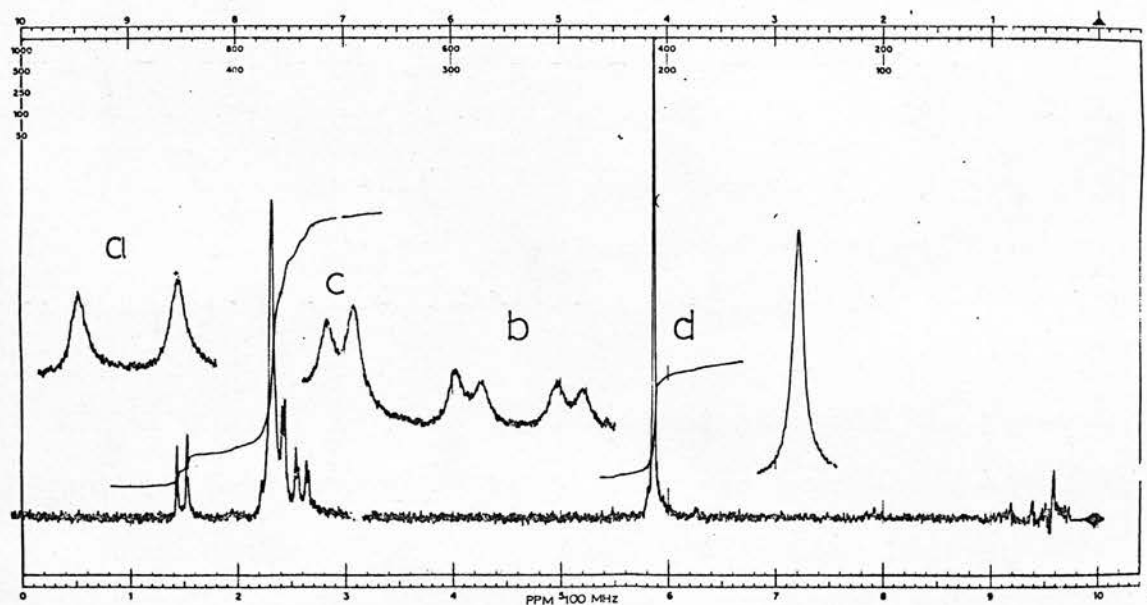


Figure 19.

¹H n.m.r. spectra of compounds (199d) (Figure 18) and (202c) (Figure 19) in trifluoroacetic acid at 170 MHz; inset expansions to 250 Hz.

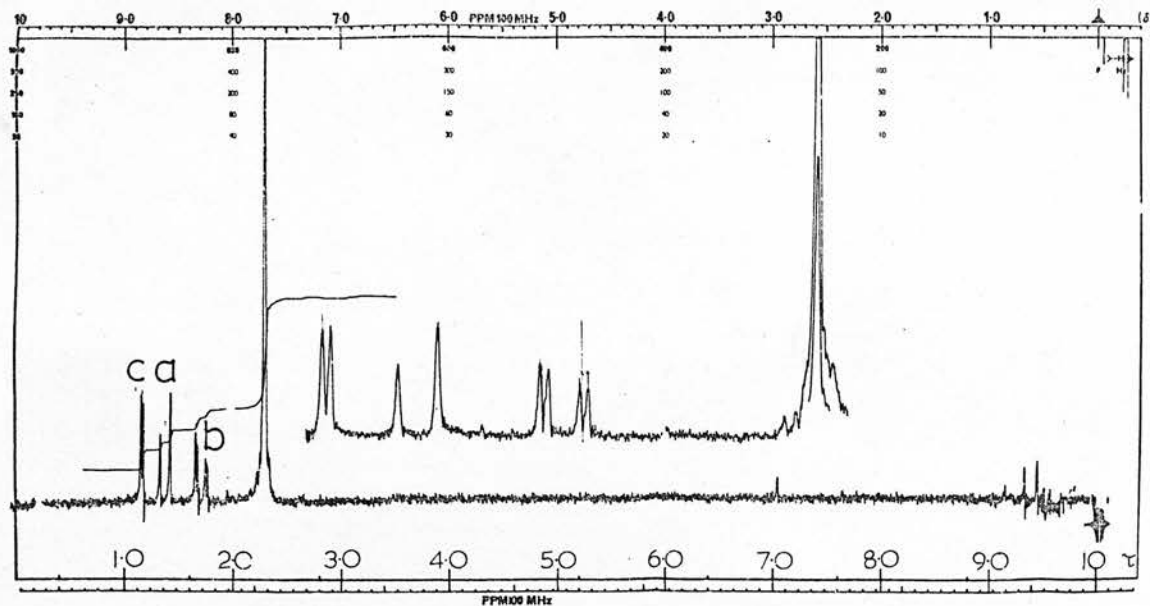


Figure 18.

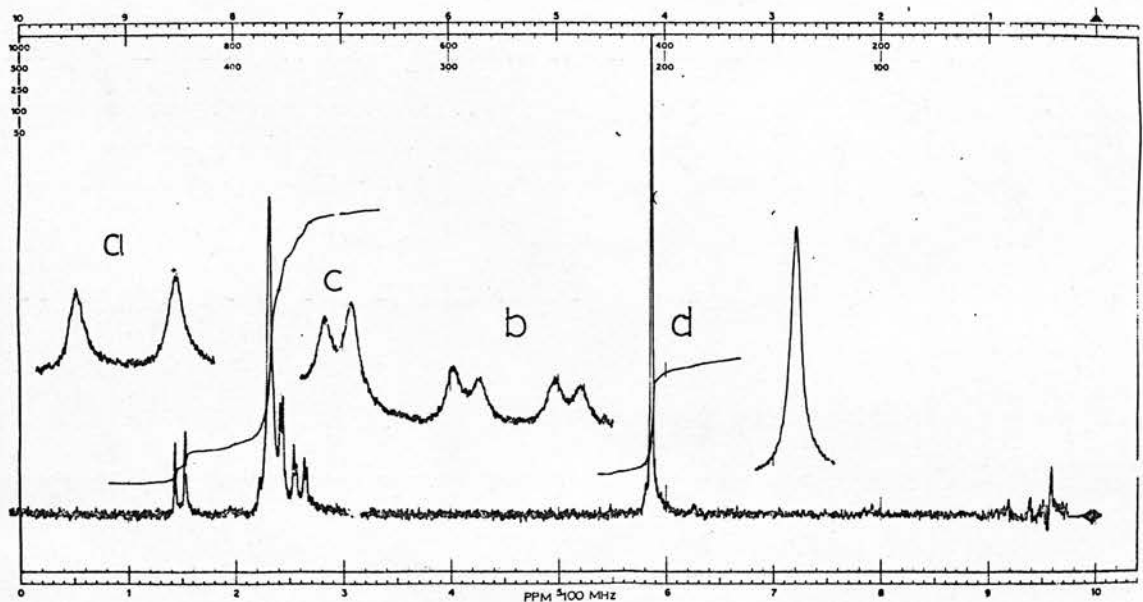
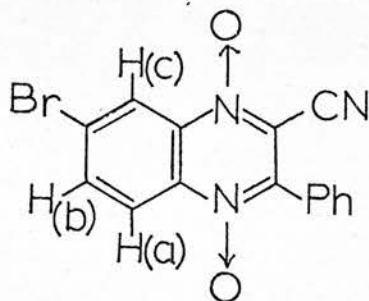
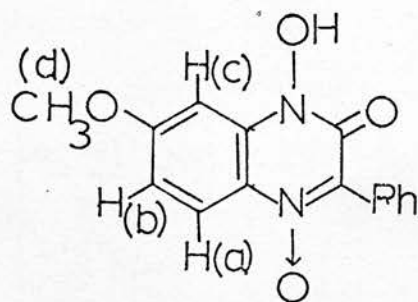


Figure 19.



^1H n.m.r. spectra of compounds (199d) (Figure 18) and (202c) (Figure 19) in trifluoroacetic acid at 100 MHz; inset expansions to 250 Hz.

component on the benzofuroxan. The essential question here is whether attack occurs at N(1) or N(3).

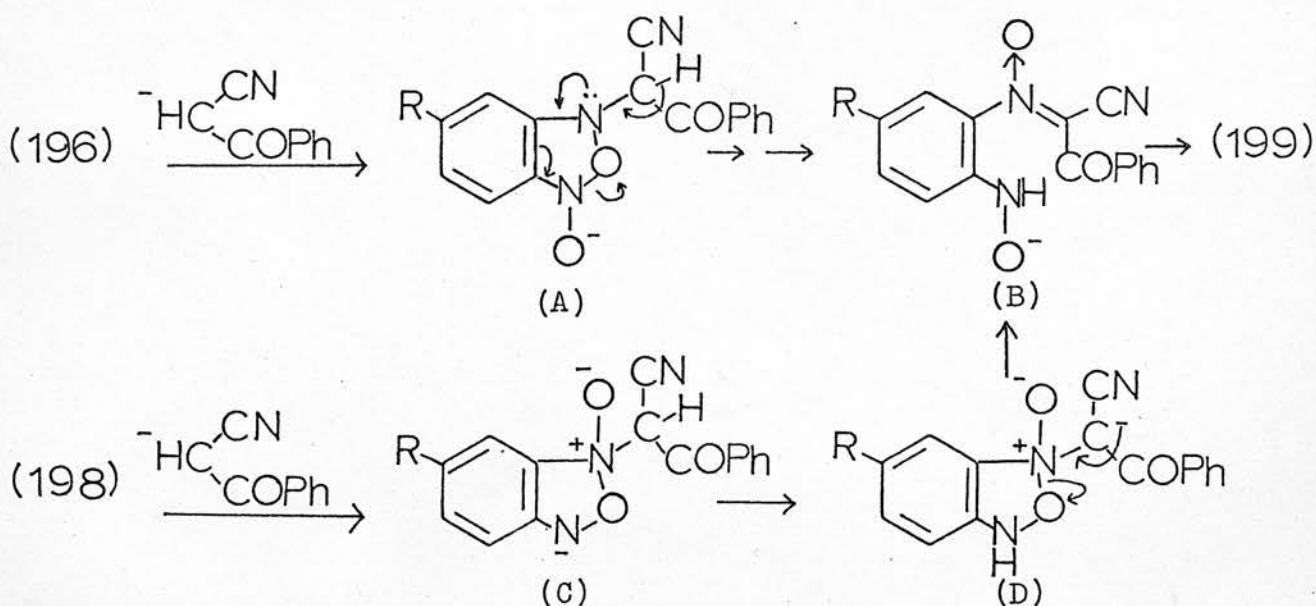
As already mentioned, Ley et al.¹⁵¹ have described the formation of quinoxaline 1,4-di-N-oxides by the base-catalysed condensations of substituted benzofuroxans with active methylene compounds. However, these authors did not indicate whether the products of these reactions are single substances or isomer mixtures, as would be expected for 5(6)-substituted benzofuroxans and for unsymmetrical methylene compounds (see above). More recently, however, Haddadin¹⁶⁰ has reported that the condensation of benzofuroxan (52; R=H) with aroylacetonophenones, or the condensation of substituted benzofuroxans with dibenzoylmethane, leads to the formation of isomeric mixtures of quinoxaline 1,4-di-N-oxides.

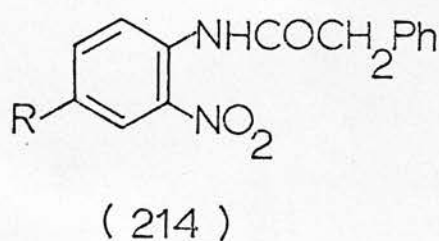
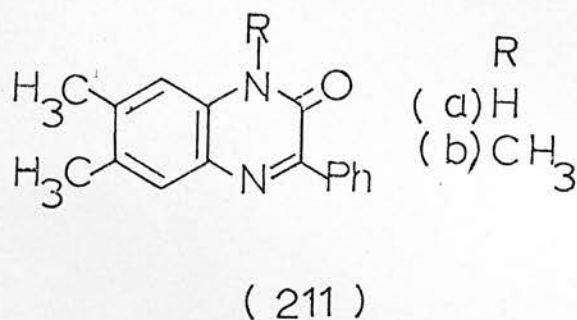
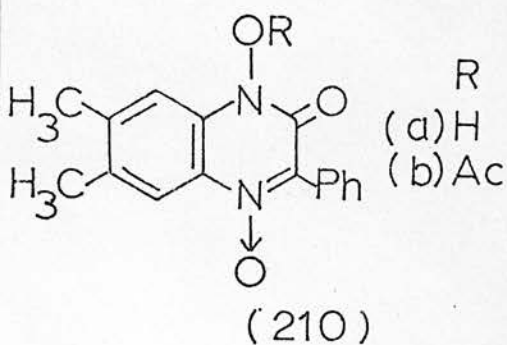
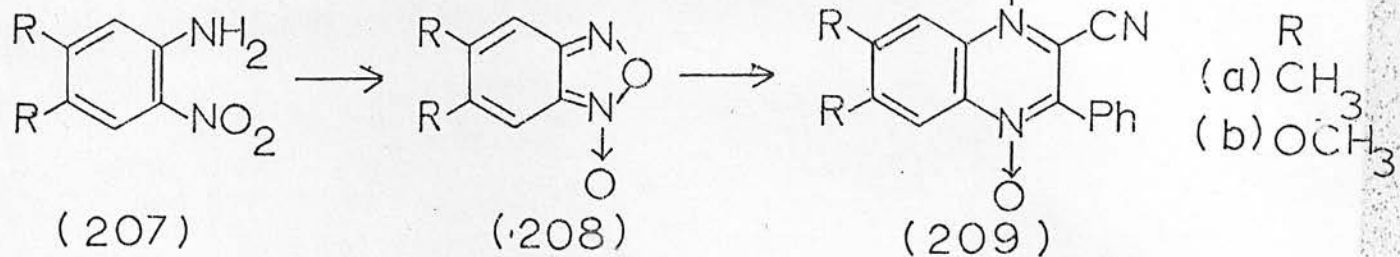
The substituted benzofuroxans (196b-e) condensed readily with benzoylacetonitrile in ethanolic ammonia to give in each case a single quinoxaline 1,4-di-N-oxide. The i.r. spectra of the products derived from (196c) (Figure 17) and (196d-e) possessed cyano-absorption at 2250 cm^{-1} . Careful examination of the ^1H n.m.r. spectra (Table 4) of the crude products showed no trace of a second isomer (see Figure 18). The quinoxaline 1,4-di-N-oxides so obtained are assigned the 6-substituted structures (199) rather than the 7-substituted structures (200) on the basis of their stepwise transformation (see below) into quinoxalones (204) of established orientation. The splitting pattern and the magnitude of the coupling constants obtained by first order analysis of

the ^1H n.m.r. spectra (Table 4 and Figure 18) are consistent with the structures (199). Similarly the reaction of 5-methylbenzofuroxan with acetylacetone afforded a single product, as shown by its ^1H n.m.r. spectrum, T.L.C. and sharpness of melting point. This compound is formulated as the 6-methyl-di-N-oxide (206) by analogy with the products obtained from benzoylacetonitrile.

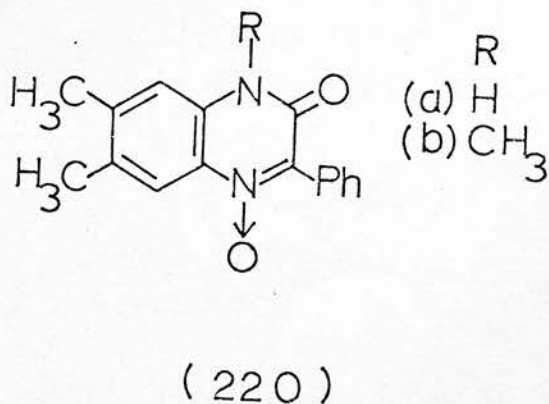
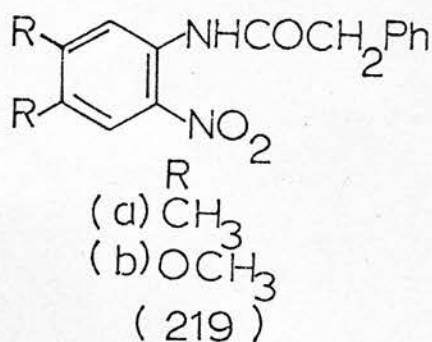
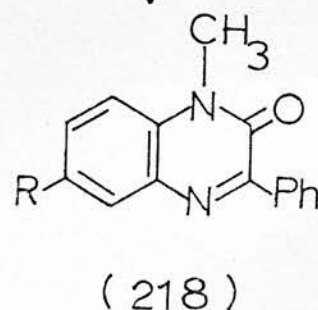
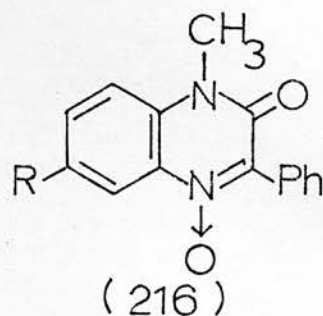
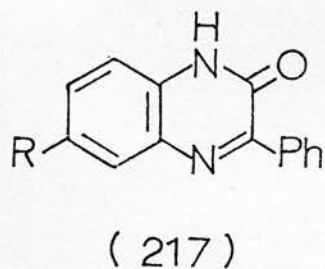
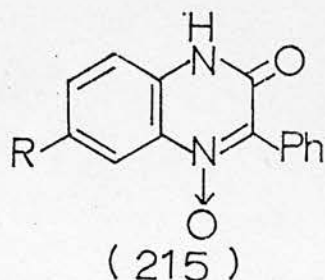
These condensations of substituted benzofuroxans with active methylene compounds to afford single products throws some light on the possible mechanism (Scheme 4) of the reaction. Haddadin's observation of the formation of isomeric products from unsymmetrical dicarbonyl compounds fits this scheme if one assumes that free rotation about the $\text{C}=\text{N}$ bond in the nitron intermediate (B) is possible. However, his reported formation of isomeric products from the condensation of substituted benzofuroxans and dibenzoylmethane¹⁶⁰ remains unexplained.

Scheme 4





- R
 (a) H
 (b) CH_3
 (c) OCH_3
 (d) Br
 (e) Cl
 (f) NO_2



Nucleophilic attack at N(3) in the benzofuroxans (196) followed by ring opening of the resulting adducts (A) and cyclisation of the hydroxylamino-nitrone intermediates (B) formed, is a possible course for formation of the di-N-oxides (199).

This is in agreement with reaction of a 5(6)-substituted benzofuroxan in its more stable tautomeric form. Alternatively the intermediates (B) could be derived by specific nucleophilic attack of the enolate anion at N(1) and subsequent cleavage of the N(1)-O(2) bond [(198) \rightarrow (C) \rightarrow (D) \rightarrow (B)] to yield the di-N-oxides (199). However, this second possibility requires reaction of a 5(6)-substituted benzofuroxan in the less stable form (198). The formation of 6-substituted di-N-oxides can also be accounted for by preferential nucleophilic attack at the 3-nitroso group in the dinitroso compounds (197). It is most unlikely however that a substituent (particularly a halogen atom) would deactivate the 4-nitroso group sufficiently to account for the predominant attack at the 3-nitroso group which would be required to explain the observed orientation in the products.

The 5,6-dimethylbenzofuroxan (208a) also reacted smoothly with benzoylacetonitrile in ethanolic ammonia to afford the corresponding 6,7-dimethyl-di-N-oxide (209a). Because of its insolubility, however, the 5,6-dimethoxybenzofuroxan (208b) contaminated the di-N-oxide product obtained by the ethanolic ammonia procedure and the two compounds were inseparable by crystallisation. The synthesis of the compound (209b) was successfully accomplished by stirring the two reagents in dimethylformamide with piperidine

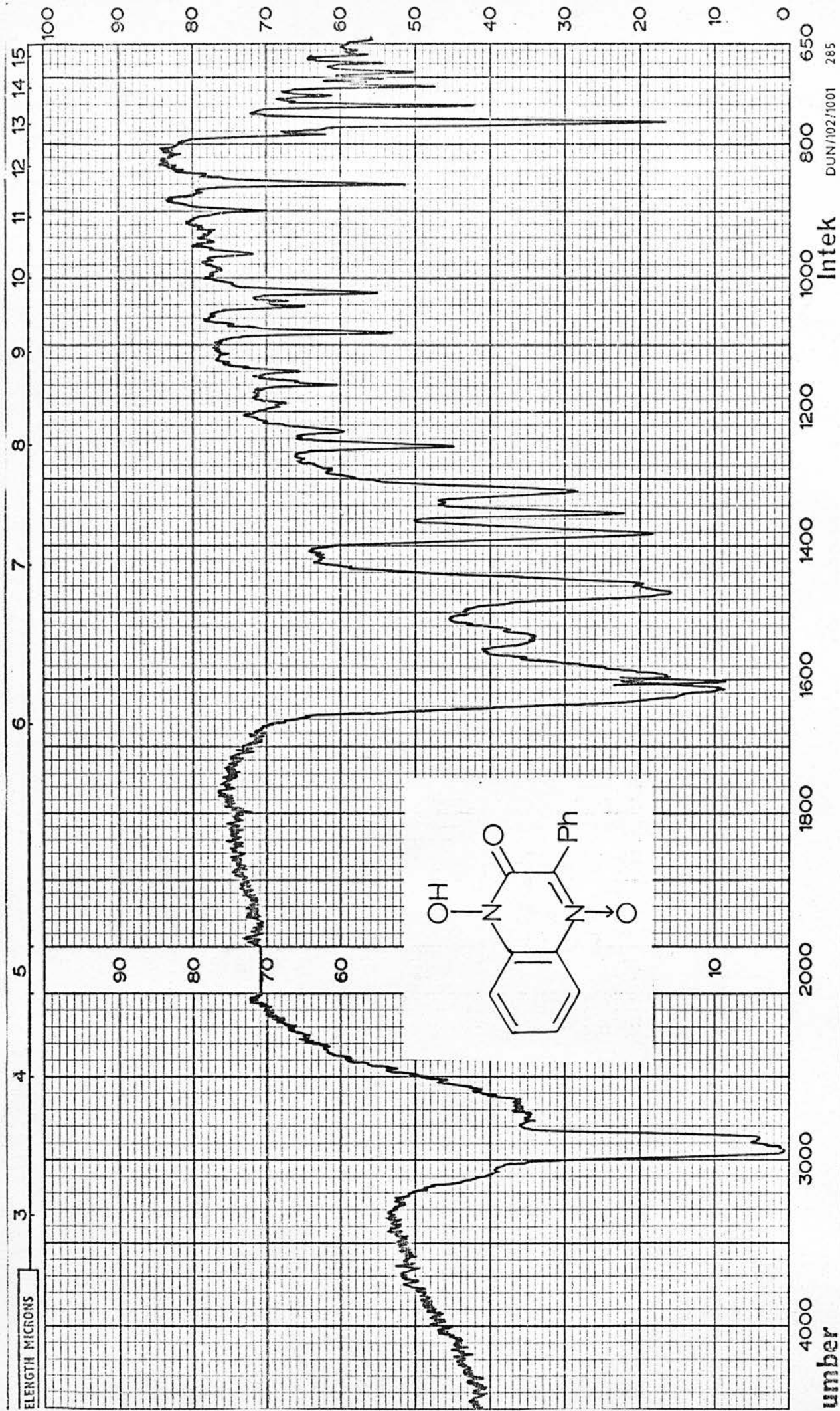
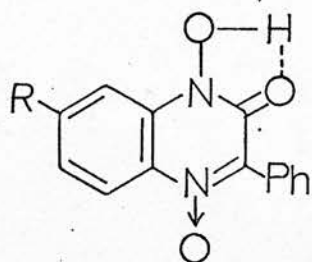


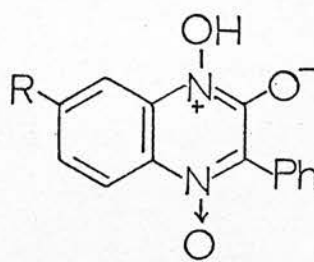
Figure 20.

as catalyst.

The substituted di-N-oxides (199b-e) and (209a) were smoothly converted into the corresponding cyclic hydroxamic acids (202b-e) and (210a), as before, by heating them with ethanolic sodium ethoxide. The di-N-oxides (199b), (199d) and (209a) did not react completely and a small amount of unchanged starting material was recovered from the reaction mixture. In the case of the di-N-oxide (199c), concomitant hydrolysis of the cyano-group occurred and the amide (201c) was isolated as a by-product. The structure of the latter product was verified by its formation from the cyano-di-N-oxide (199c) by hydrolysis with concentrated sulphuric acid. The cyclic hydroxamic acids (202b-e) and (210a) all gave the characteristic deep red colour¹⁵² with iron (III) chloride in ethanol (see before), and all formed N-acetoxy derivatives (203b-e) and (210b) with characteristic i.r. bands¹⁴⁸ at $1800-1785\text{ cm}^{-1}$ (cyclic:N·OAc). With the exception of the compounds (202c-d), the carbonyl stretching frequency due to the cyclic hydroxamic group (N·OH-C=O) was lowered to about 1600 cm^{-1} (see Figure 20). This is most probably due to hydrogen bonding within the cyclic hydroxamic acid group, as shown in the structure (212), or to the effects of the contributing zwitterionic structure (213).



(212)



(213)

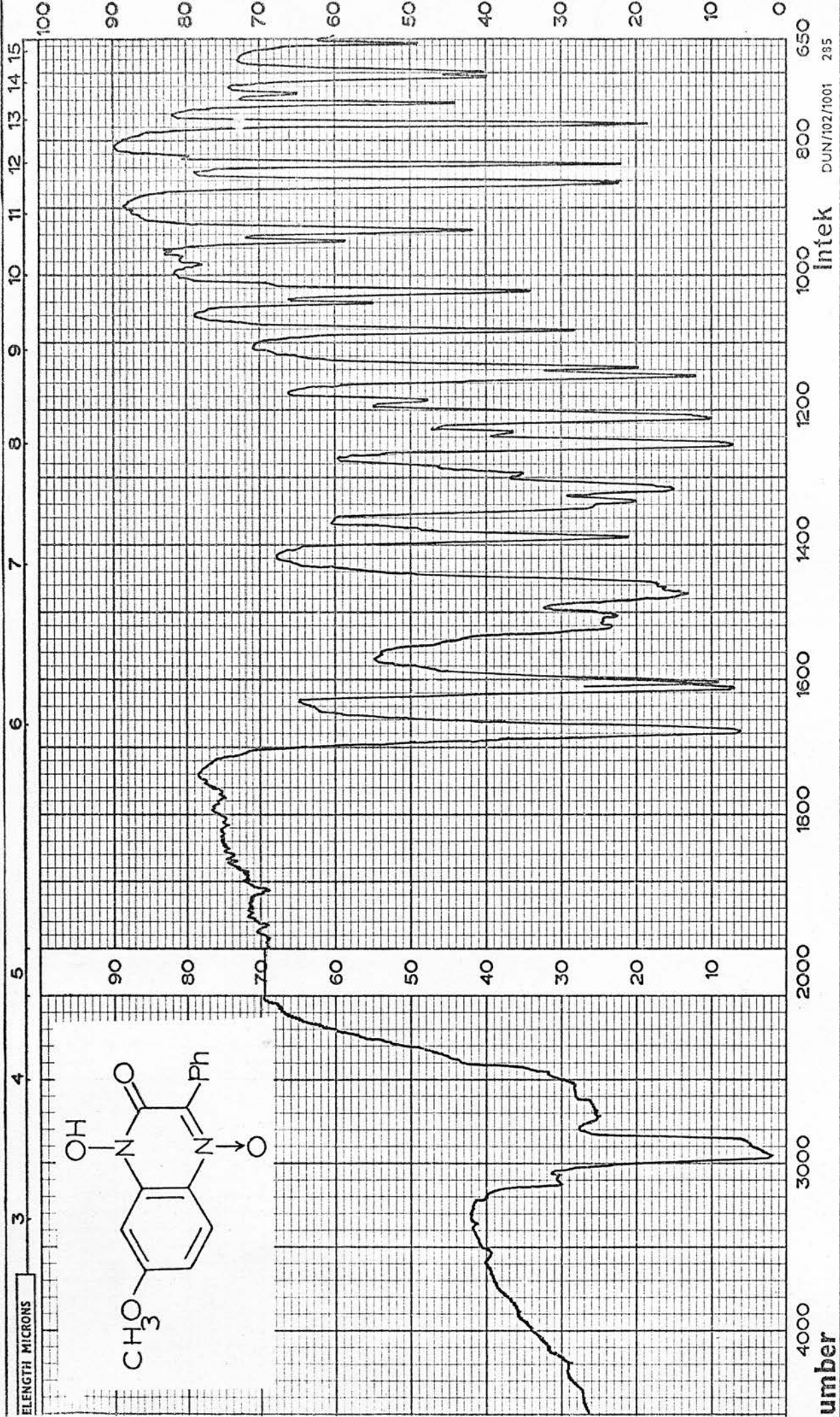


Figure 21.

The methoxy-derivative (202c) (Figure 21) and the bromo-derivative (202d), however, have higher carbonyl absorptions ($1670\text{--}1650\text{ cm}^{-1}$). The gross structure and orientation of the substituted cyclic hydroxamic acids were established by reduction. On treatment with sodium dithionite, the dimethyl cyclic hydroxamic acid (210a) afforded the dimethylquinoxalin-3(4H)-one (211a), prepared by a different route (see below), both the N-hydroxy and N-oxide groups being reduced. This confirmed the presence of the quinoxalin-3(4H)-one nucleus. Reduction of the mono-substituted cyclic hydroxamic acids (202b-e) afforded good yields of compounds which were non-identical (i.r. and n.m.r. spectra, depression of mixed m.p.) (e.g. Figures 22 and 23), with the 7-substituted quinoxalin-3(4H)-ones (217b-e) of known orientation¹⁴⁹ (prepared as described below). By virtue of their mode of synthesis, the quinoxalones derived by reduction of the cyclic hydroxamic acids (202b-e) can only be 6- or 7-substituted derivatives. Since they are not identical with the known 7-substituted compounds (217b-e) they are assigned the 6-substituted structures (204b-e). This was further confirmed by the methylation of the quinoxalone obtained by reduction of the methoxy hydroxamic acid (202c). The product of methylation was shown to be identical with 6-methoxy-4-methylquinoxalin-3(4H)-one (246b) prepared by a different route (see above). On this basis the cyclic hydroxamic acids and hence the cyano di-N-oxides are assigned the structures (202b-e) and (199b-e), respectively. The first-order analysis of the splitting pattern and the magnitude of the coupling constants in the

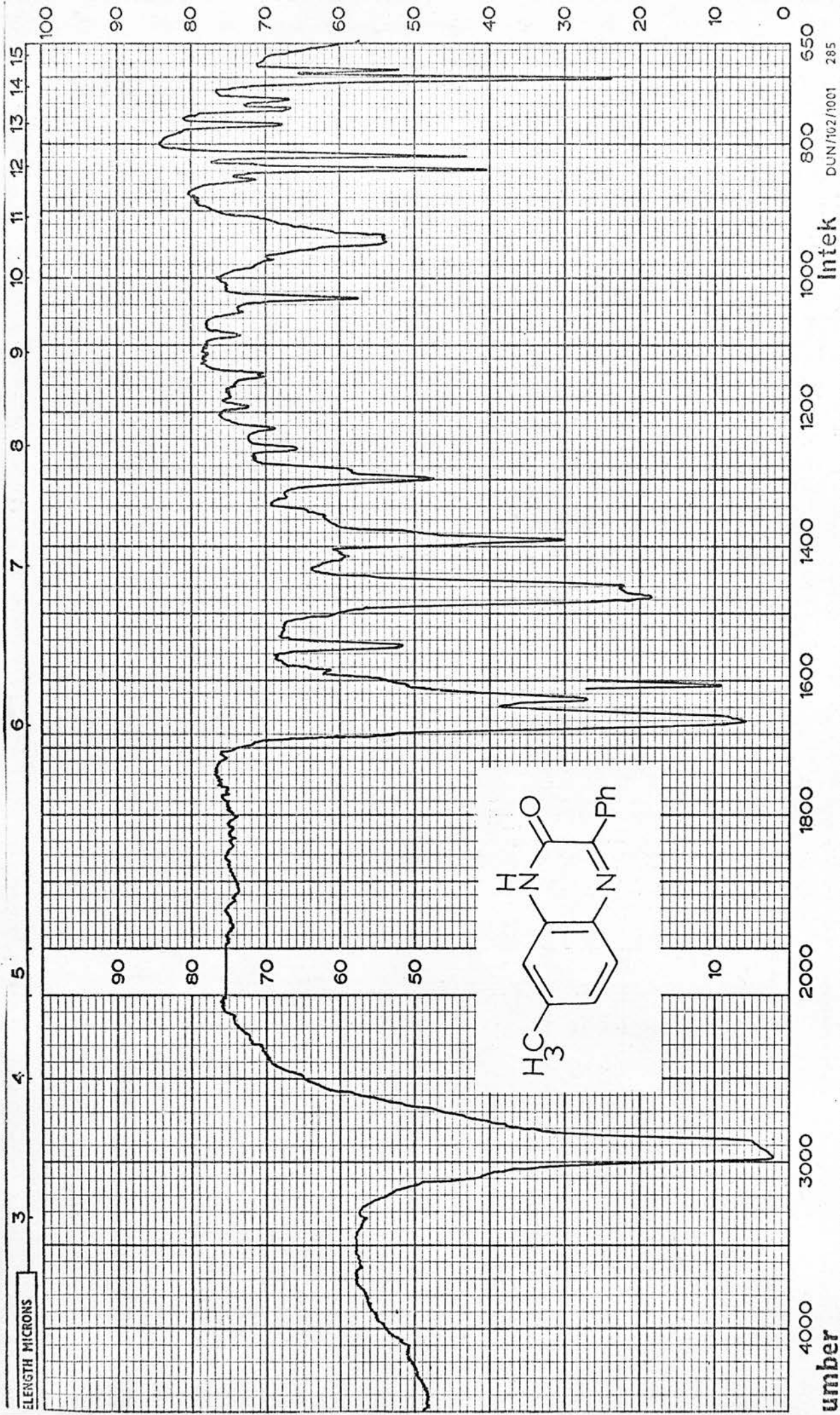


Figure 22.

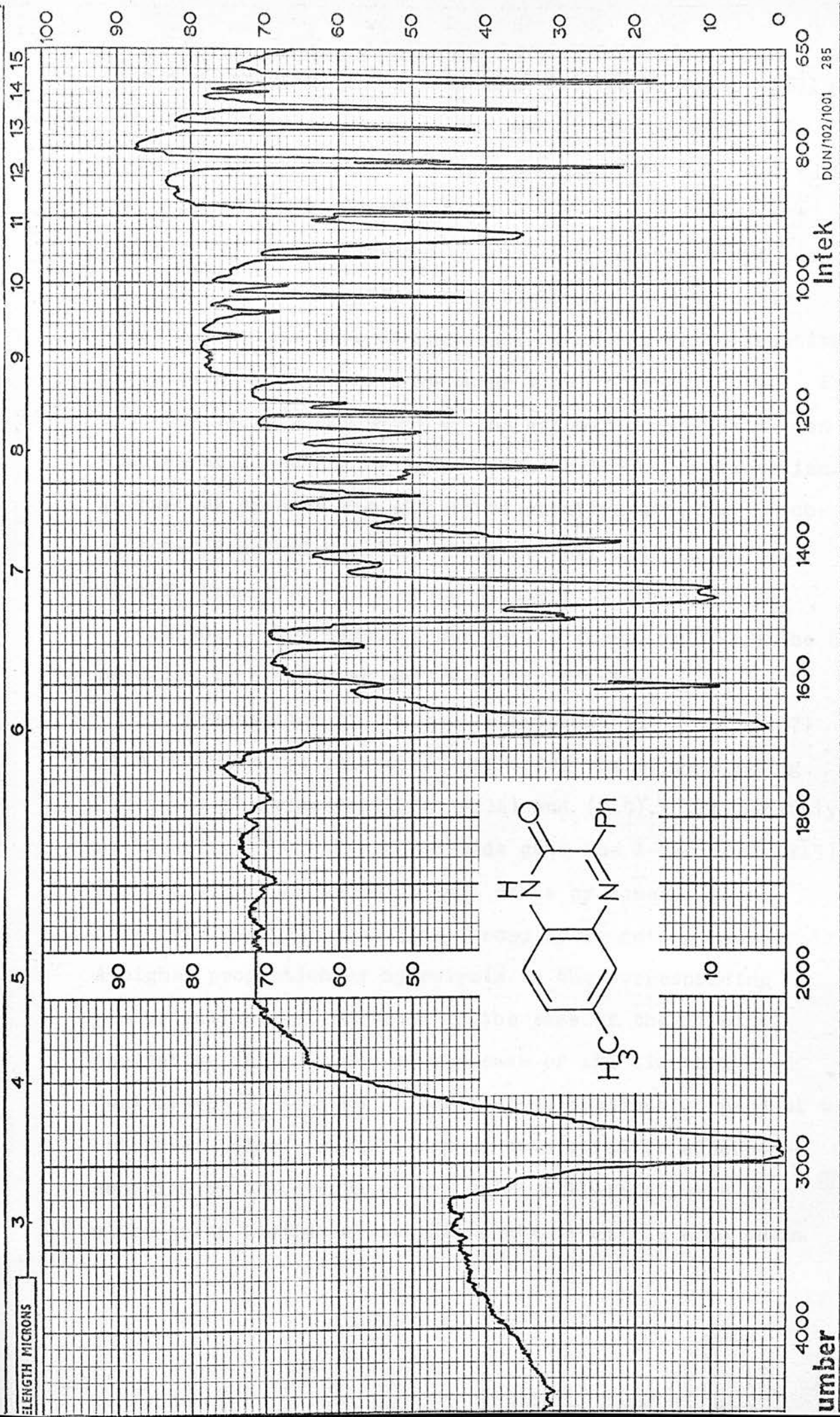
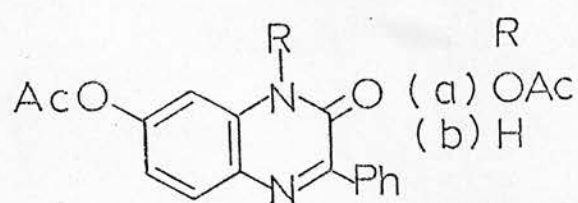


Figure 23.

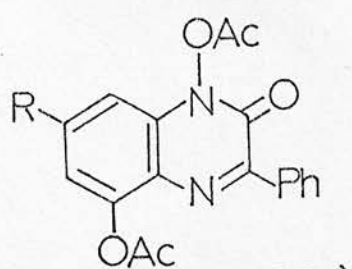
^1H n.m.r. spectra of the compounds (199)(e.g. Figure 18), (202)(e.g. Figure 19) and (204) are in full accord with these structure assignments (see Tables 3 and 4).

Since the hydroxamic acids (202b-e) and (210a) are substituted in the 6-position, attack by acetic anhydride at this position is effectively blocked. Consequently these substrates were of particular interest since substitution, if successful would have to occur at a different site. The alternative site for entry of the acetoxy-group would then provide evidence for, or against, the nucleophilic mechanism. To further examine the effects of substituents, the 7-substituted N-methyl-N-oxides (216b-f) were synthesised to observe the effect of a group adjacent to the reactive 6-position. The dimethyl-derivative (220b) in which the 6-position is blocked as well was also obtained.

Condensation of the o-nitroanilines (195) and (207) with phenylacetyl chloride¹⁴⁸ afforded the corresponding 2-nitro- α -phenylacetanilides (214) and (219). Base-catalysed cyclisation¹⁴⁹ of these compounds gave the 1-N-oxides (215) and (220a), accompanied in some cases by some of the corresponding o-nitroaniline formed by competing hydrolysis. A higher proportion of hydrolysis to the corresponding o-nitroaniline was observed in the case of the dimethyl derivative (219a) while in the case of the dimethoxy derivative (219b) none of the desired cyclisation product was obtained. These results can be attributed to electron-donation by the 5-substituent which will deactivate the nitro group towards nucleophilic attack by the side chain

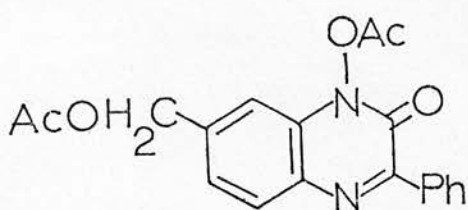


(221)

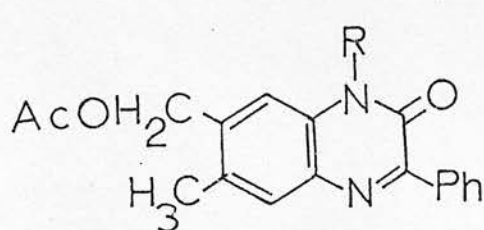


(222)

R
(a) CH₃
(b) OCH₃
(c) Br
(d) Cl

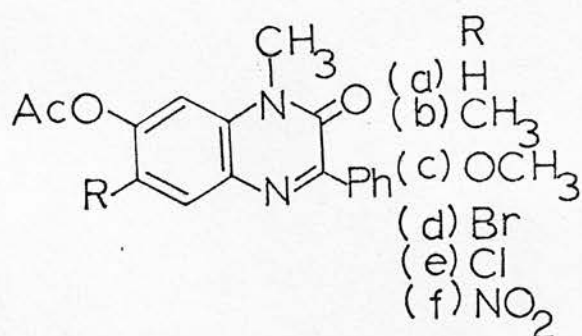


(223)

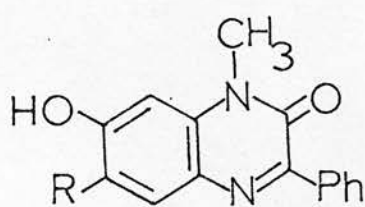


(224)

R
(a) OAc
(b) CH₃
(c) H

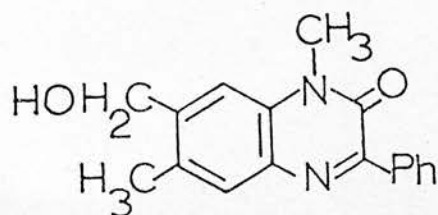


(226)



(227)

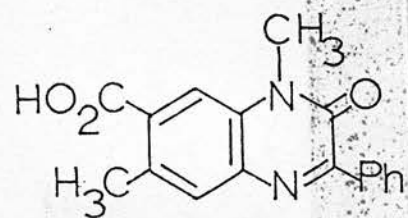
R
(a) H
(b) CH₃
(c) OCH₃



(228)



(229)



(230)

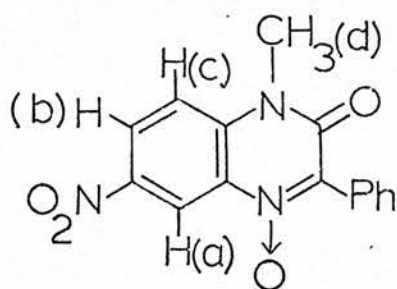
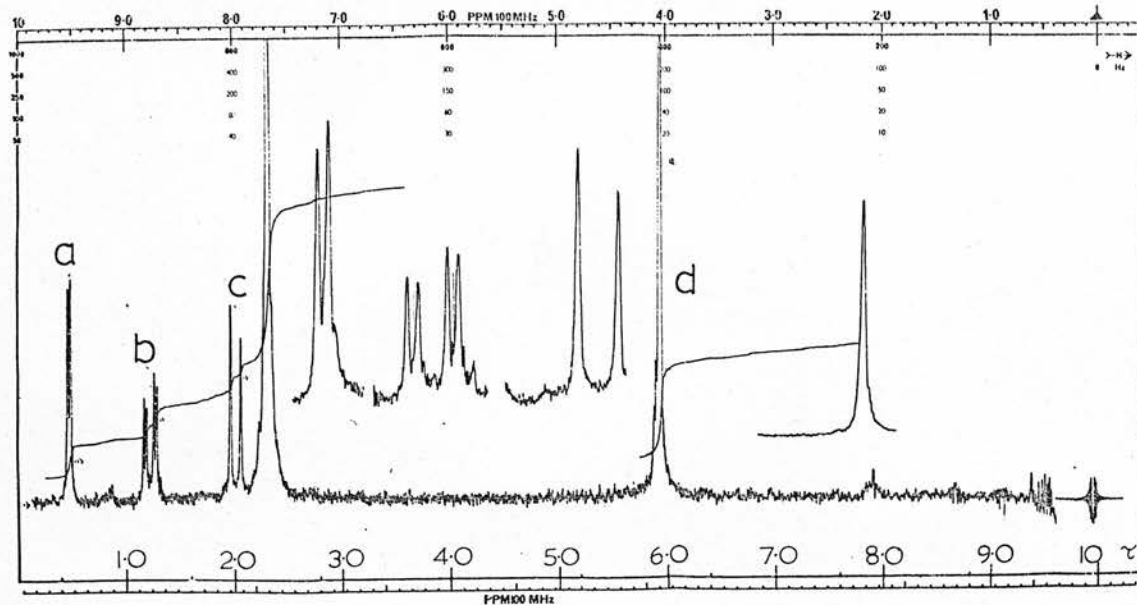


Figure 24.

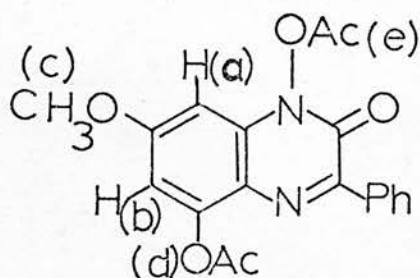
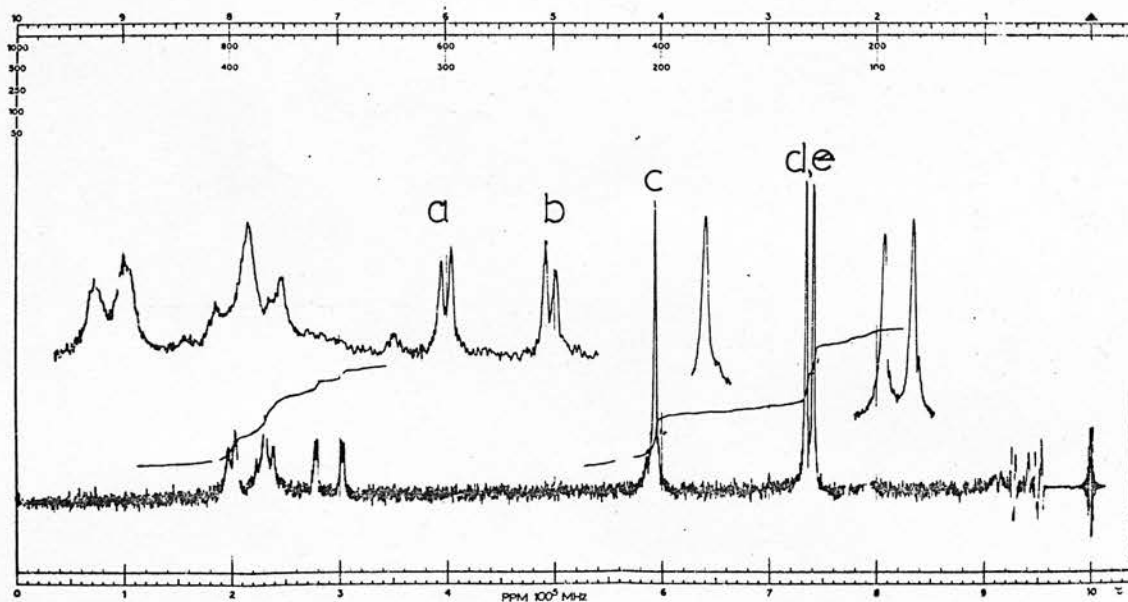


Figure 25.

^1H n.m.r. spectra of compounds (216f) (Figure 24) and (222b) (Figure 25) in trifluoroacetic acid at 100 MHz; inset expansions to 250 Hz.

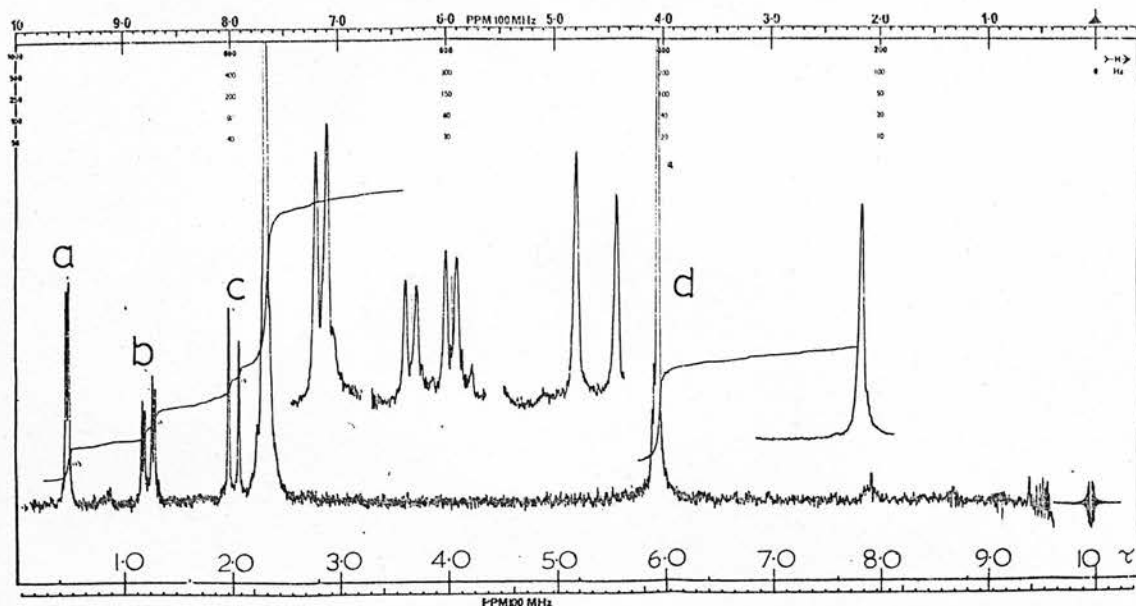


Figure 24.

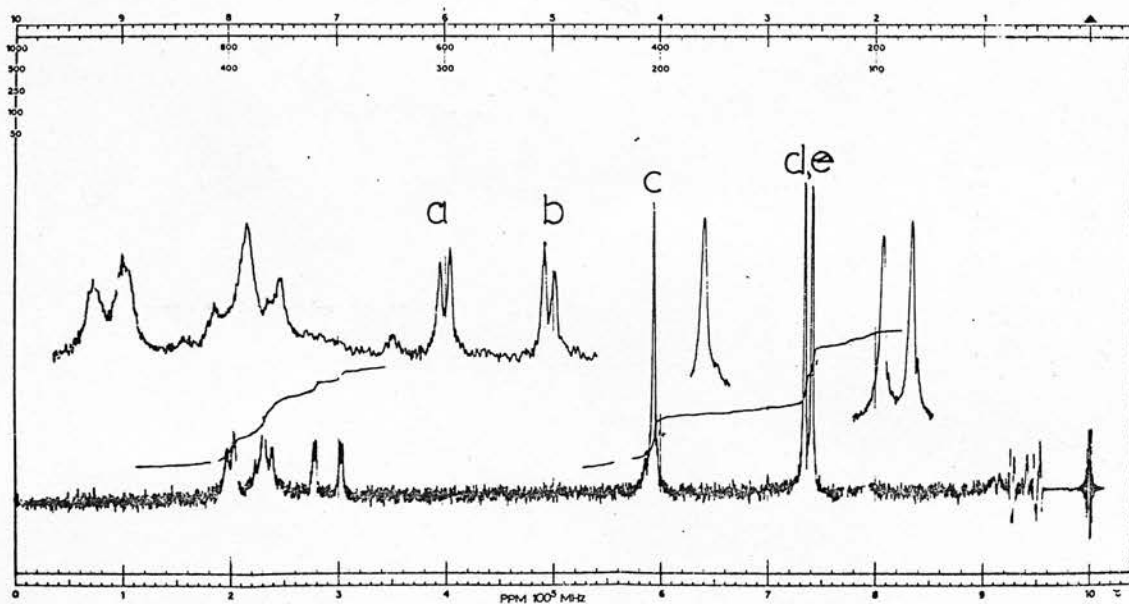
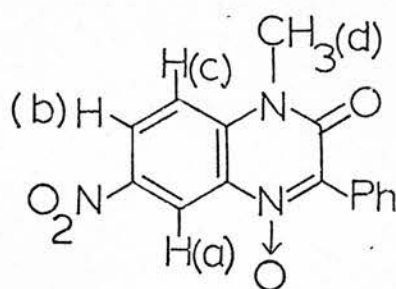


Figure 25.



^1H n.m.r. spectra of compounds (216f) (Figure 24) and (222b) (Figure 25) in trifluoroacetic acid at 100 MHz; inset expansions to 250 MHz.

and hence will tend to inhibit cyclisation.

Dithionite reduction of the N-oxides (215b-e) afforded the 7-substituted quinoxalin-3(4H)-ones (217b-e) which were non-identical (see above) with the reduction products of the cyclic hydroxamic acids (202b-e). Similar reduction of the dimethyl N-oxide (220a) afforded the quinoxalone (211a).

Methylation of the 1-N-oxides (215) and (220a) with dimethyl sulphate in 10% aqueous sodium hydroxide afforded the corresponding N-methyl derivatives (216) and (220b) which were converted by dithionite reduction into the N-methyl-quinoxalin-3(4H)-ones (218) and (211b). 7-substituted structures for these compounds are established by their mode of synthesis and by the splitting patterns present in their ^1H n.m.r. spectra (see Table 3 and Figure 24).

On prolonged heating with acetic anhydride, the substituted cyclic hydroxamic acids (202c-e) afforded products which analysed correctly as diacetoxy derivatives of the corresponding reduced quinoxalin-3(4H)-ones (204c-e). The i.r. spectra of these products contained strong absorption bands at 1800 and 1780-1760 cm^{-1} (c.f. Figure 16) indicating the presence of N-acetoxy and C-acetoxy groups respectively. A third strong absorption at 1680 cm^{-1} is attributable to the carbonyl group of a quinoxalin-3(4H)-one no longer hydrogen-bonded. The ^1H n.m.r. spectrum of the product obtained from the methoxy compound (202c) (Table 6 and Figure 25) contains two signals near τ 7.4 each integrating for three protons. The absence of these signals from the spectrum of the parent compound (202c) (Figure 19) permits

their assignment to the methyl protons of the two acetoxy-groups. The aromatic region of the spectrum contains two doublets, each integrating for one proton, whose coupling constants are of the order of 2.25 Hz. This demonstrates that there are two meta-coupled protons present in a benzene ring. Since the 6-position for the methoxy-group can be assumed this pattern can only be accommodated by the introduction of the acetoxy-group into the 8-position of the quinoxaline nucleus. The ^1H n.m.r. spectra of the products derived from the cyclic hydroxamic acids (202d-e) (Table 6) were of a closely similar nature. Consequently these compounds are formulated as the 4,8-diacetoxy-2-phenyl-quinoxalin-3(4H)-ones (222b-d). No trace of products derived by ring contraction (see before), or by an alternative substitution pattern, could be detected in these reactions. Entry of an acetoxy-group into the 8-position when the 6-position is blocked provides strong support for the nucleophilic nature of the process.

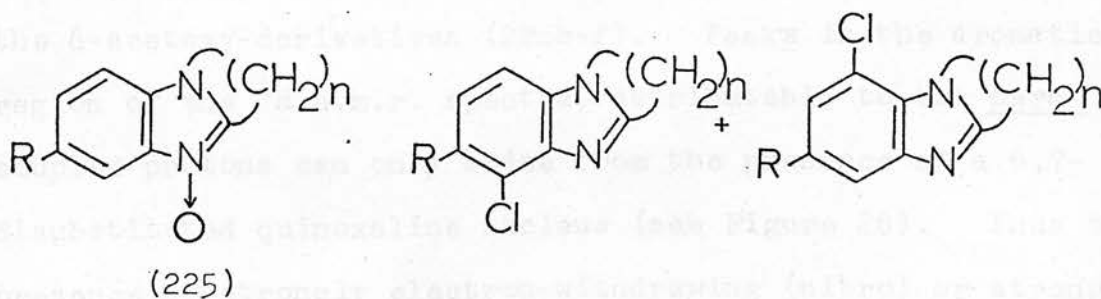
The product obtained by heating the methyl compound (202b) with acetic anhydride showed properties which were not in accord with those expected for the acetoxy-compound (222a). The product obtained analysed correctly for a diacetoxy-derivative but the ^1H n.m.r. spectrum (Table 6) showed signals due to only two rather than [see structure (222a)] three methyl groups. However the presence of a signal at τ 4.52 corresponding to two protons indicated that in this case, acetoxylation had occurred at the 6-methyl group (cf. Figure 27) and not at the 8-position in the ring, to give (223).

Although it is well known that methyl groups at a carbon atom adjacent to an N-oxide group undergo acetoxylation (cf. the reaction of picoline N-oxides with acetic anhydride, pp.24-6) this appears to be the first recorded example of acetoxylation at a methyl group positioned on an adjacent fused benzene ring.

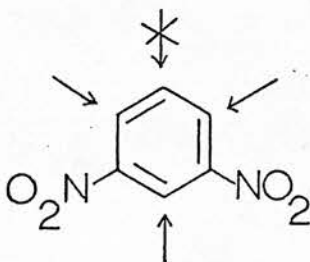
In a similar manner the dimethyl cyclic hydroxamic acid (210a) also yielded an acetoxymethyl derivative which is formulated as the 6-acetoxymethyl compound (224a) by analogy with the compound (223). Presumably in this case the steric effect of a 7-methyl group is an additional factor making the tendency for substitution to occur at the 8-position less likely.

Prolonged heating of the 2-cyano-hydroxamic acid (193a) with acetic anhydride only afforded the N-acetoxy derivative (193b) showing the greater resistance of this molecule to substitution.

In a recent publication, Suschitzky and his coworkers¹⁶¹ claim that 1,2-polymethylenebenzimidazole N-oxides (225) are substituted in the benzene ring by the combined action of an acid chloride and various nucleophiles (e.g. chloride ion), at positions corresponding to the 5- and 8-positions of the quinoxaline nucleus.



Substitution in the 5-position is apparently most marked for the nitro-benzimidazole N-oxides (225; $R=NO_2$). This observation is of importance in connection with our studies because of the similarity between the benzimidazole N-oxides (225) and the 7-substituted 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxides (216). It is difficult to understand how substitution can occur at the 5-position with the nitro-benzimidazole N-oxide (225; $R=NO_2$) because the situation is somewhat similar to that in 2,4-dinitrobenzene. With this latter molecule, nucleophilic substitution could probably occur at any of the three positions indicated but almost certainly not at the position meta- to both nitro-groups.



If Suschitzky's findings¹⁶¹ are correct then more than one mechanism must operate in this type of reaction.

Examination of the 1H n.m.r. spectra (Table 5 and Figure 26) of the products obtained from the reaction of the 7-substituted N-methyl compounds (216b-f) with acetic anhydride, showed that without exception, these products are the 6-acetoxy-derivatives (226b-f). Peaks in the aromatic region of the 1H n.m.r. spectra, attributable to two para-coupled protons can only arise from the presence of a 6,7-disubstituted quinoxaline nucleus (see Figure 26). Thus the presence of strongly electron-withdrawing (nitro) or strongly

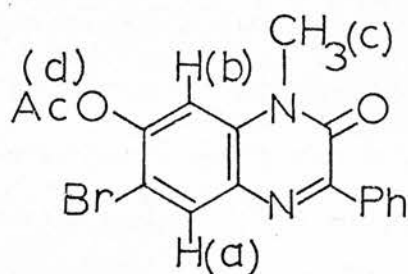
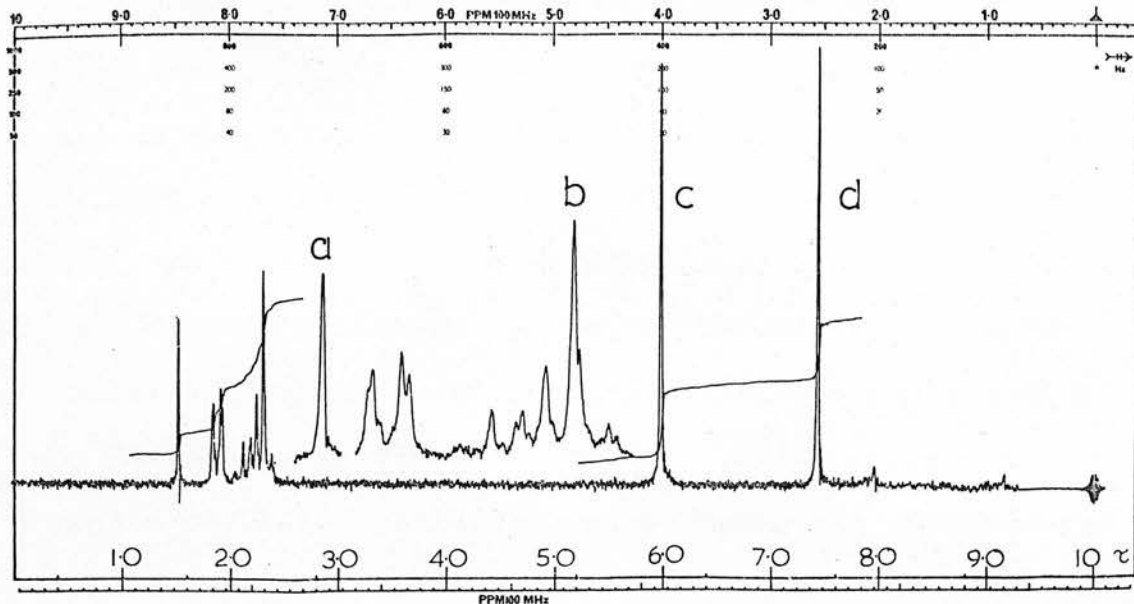


Figure 26.

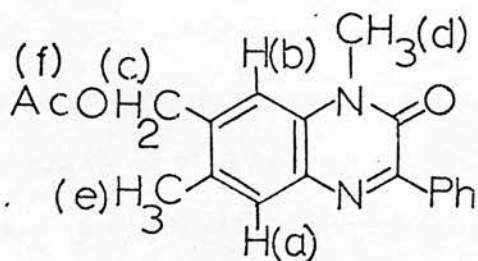
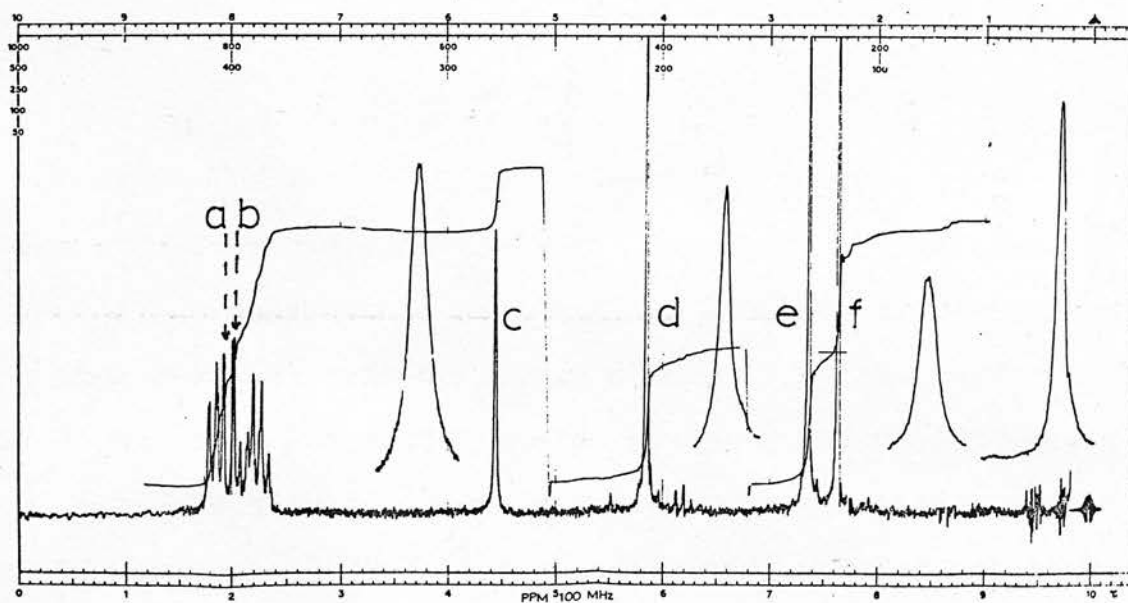


Figure 27.

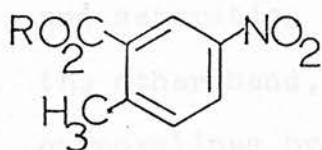
¹H n.m.r. spectra of compounds. (226d)(Figure 26) and 224b)(Figure 27) in trifluoroacetic acid at 100 MHz; inset expansions to 250 Hz.

electron-donating (methoxy) groups in the benzene nucleus appears to have little or no effect on the course of the presumed nucleophilic substitution by acetate ion. However it is clearly shown that substitution of an acetoxy group does not occur at C(5), regardless of the substituent at C(7).

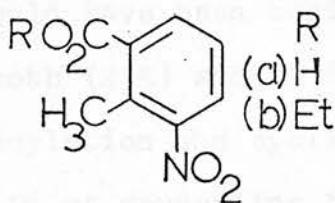
Hydrogenolysis of the acetoxymethyl compound (224a), derived from the cyclic hydroxamic acid (210a) resulted in the loss of the N-acetoxy group giving compound (224c). Methylation of the latter afforded a product identical with that obtained by treatment of the N-methyl-N-oxide (220b) with acetic anhydride. Substitution can again be shown to occur at one of the methyl groups, by the absence of a methyl group and the presence of a methylene group in the ^1H n.m.r. spectrum (Table 5 and Figure 27). The carbonyl stretching frequency ($\nu_{\text{max.}}$ 1725 cm^{-1}) of the acetoxymethyl group is also lower than the corresponding acetoxy-group directly attached to the benzene ring. Hence the product derived from the N-methyl-N-oxide (220b) and acetic anhydride is formulated as (224b) since it has been shown (see above) to have the same orientation as the acetoxymethyl derivative (224a). It is assumed, by analogy with the known reactivity of the 6-methyl group in the hydroxamic acid (202b), that the 7-methyl group in the N-oxides (210a) and (220b) remains intact. To remove any doubt as to the position of the acetoxymethyl group an attempt was made to degrade the acetoxymethyl derivative (224b) to the hydroxy-compound (227b) obtained by hydrolysis of the acetoxy-compound (226b) of known structure (see above). Hydrolysis of the acetoxy-

methyl compound (224b) afforded the corresponding hydroxymethyl derivative (228). The latter compound was treated with hydrogen peroxide and 10% aqueous sodium hydroxide in the hope that the intermediate aldehyde (229) would undergo Dakin oxidation to yield the hydroxy derivative (227b). However, the hydroxymethyl compound (228) was recovered unchanged. Attempted formation of the aldehyde (229) by manganese dioxide oxidation of the hydroxymethyl compound (228) was also unsuccessful.

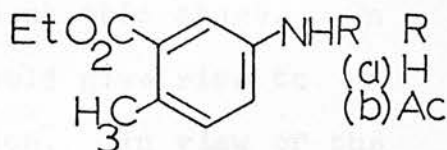
An attempt was made to synthesise the acetoxymethyl compound (224b) by way of the corresponding carboxylic acid (230) or its ester. Nitration of *o*-toluic acid¹⁶² afforded a mixture of the two isomeric nitro-compounds (231a) and (232a) shown to be in the ratio 4:3 on the basis of the ¹H n.m.r. spectrum of the mixture. Attempts to separate the two isomers by fractional crystallisation were unsuccessful. Column chromatography was not attempted because of the acidic nature of the compounds. However conversion of the mixture of acids into the corresponding ethyl esters (231b) and (232b)



(231)



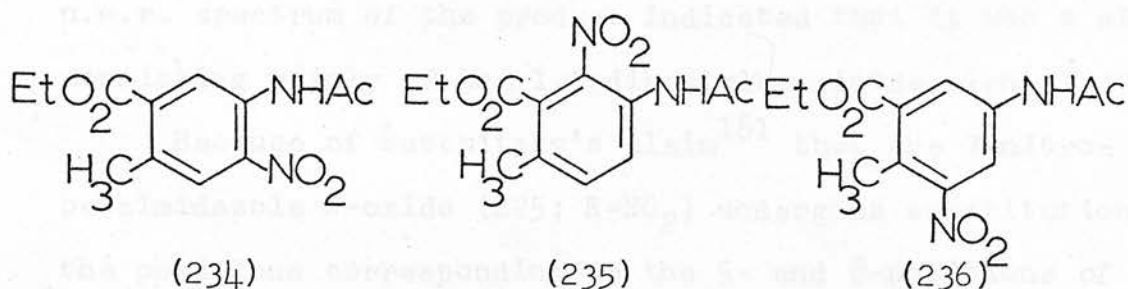
(232)



(233)

permitted separation by spinning-band distillation. Reduction of the higher-boiling isomer (231b) with iron in acetic acid afforded a mixture of the amine (233a) and its acetyl

derivative (233b). It was hoped that the acetylamino compound (233b) would nitrate specifically ortho- to the acetylamino group, whereas polynitration or a mixture of mono-nitro isomers might be expected on nitration of the amine (233a). Analysis of the ^1H n.m.r. spectrum of the nitration product of the acetylamino compound (233b) revealed the formation of all three possible mono-nitro isomers (234), (235) and (236), with the desired product (234) present in

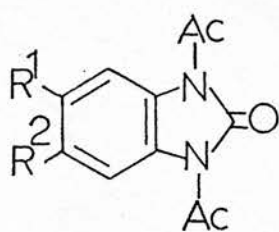


least amount. Column chromatography separated the compound (236) from the other two isomers but all attempts to separate (234) and (235) were unsuccessful. If compound (234) had been contaminated with the other isomer (236) the synthesis would have been continued because only the anilide derived from (234) and phenylacetyl chloride should undergo cyclisation and separation could have been achieved at this stage. On the other hand, both (235) and (236) would give rise to quinoxalines by acylation and cyclisation. In view of the probable difficulty of separating the resulting isomeric quinoxaline N-oxides, and principally because of the low overall yield, the synthesis was terminated at this stage.

As previously discussed, Ahmad and his coworkers¹⁴⁷ observed that the quinoxalin-3(4H)-one 1-N-oxides (187) on

reaction with acetic anhydride undergo ring contraction to the benzimidazolones (188). In the light of our discovery that a methyl group in the 6-position of a quinoxaline nucleus is prone to acetoxylation when the compound is heated with acetic anhydride, the dimethyl N-oxide (220a) was treated with acetic anhydride. However, the ^1H n.m.r. spectrum of the crude product contained no trace of a methylene signal, so it is assumed that ring contraction occurred. The ^1H n.m.r. spectrum of the product indicated that it was a mixture consisting mainly of the 1,3-diacetylbenzimidazolone (237a).

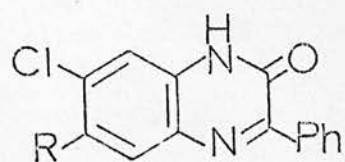
Because of Suschitzky's claim¹⁶¹ that the 7-nitrobenzimidazole N-oxide (225; $\text{R}=\text{NO}_2$) undergoes substitution in the positions corresponding to the 5- and 8-positions of the quinoxaline nucleus (see above); the reaction of the 7-nitro N-oxide (215f) with acetic anhydride was studied. Only the expected ring contraction occurred to yield the benzimidazolone (237b).



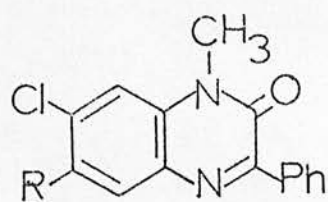
(237)

	R^1	R^2
(a)	CH_3	CH_3
(b)	H	NO_2

Thus, in their reactions with acetic anhydride, the quinoxalin-3(4H)-one 1-N-oxides possessing a hydroxyl group or a methyl group at N(4), undergo acetoxylation of the fused benzene ring or at a 6-methyl group. Those possessing a free hydrogen atom at N(4) undergo ring

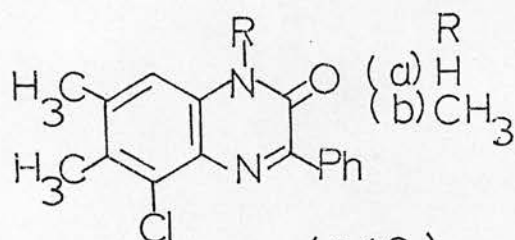


(238)



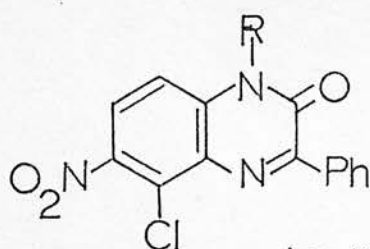
(239)

- (a) R
(b) H
(c) CH₃
(d) OCH₃
(e) Br
(f) Cl
(f) NO₂



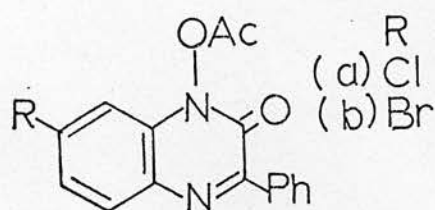
(240)

- (a) R
(b) H
(b) CH₃



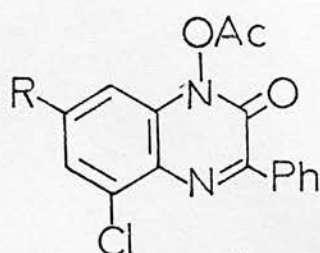
(241)

- (a) R
(b) CH₃



(242)

- (a) R
(a) Cl
(b) Br

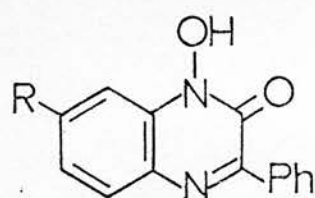


(243)

- (a) R
(a) CH₃
(b) OCH₃
(c) Br
(d) Cl

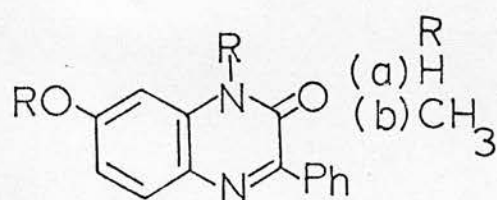


(244)



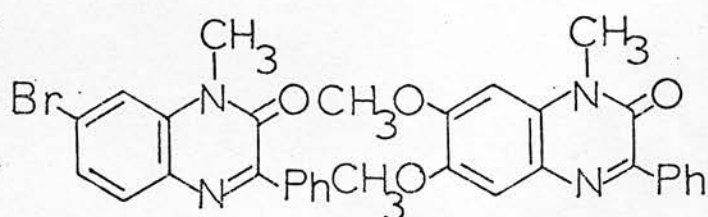
(245)

- (a) R
(a) H
(b) Cl



(246)

- (a) R
(a) H
(b) CH₃



(247)

(248)

contraction to benzimidazolones. In contrast, only substitution in the benzene ring has been observed for the reaction of the quinoxalin-3(4H)-one N-oxides (215) and (216) with acetyl chloride. This type of reaction was studied in greater detail to discover the effect of substituents in the benzene ring, and of the presence of a second oxygen function at N(4). Without exception, treatment of the 7-substituted-2-phenylquinoxalin-3(4H)-one 1-N-oxides (215b-e) and (216b-e) with acetyl chloride in acetic acid resulted in chlorination at C(6) to afford the chloro-derivatives (238b-e) and (239b-e), respectively. That both types of N-oxide (215) and (216) underwent the same type of reaction was shown by methylation of the products (238b-e) to give methyl-derivatives (239b-e) identical with the products of the reaction of the N-methyl-N-oxides (216b-e) with acetyl chloride. The orientation of these chloro-derivatives is supported by their ^1H n.m.r. spectra (Table 5) which contain two para-coupled protons in a benzene ring (see Figure 28) showing them to be 6,7-disubstituted quinoxalin-3(4H)-ones. The product obtained from reaction of the N-oxide (215a) with acetyl chloride was identical with the product of reduction of the chloro-hydroxamic acid (202e), adding further support to the orientation assigned to the compounds (202).

By analogy with the results obtained from the reactions of the dimethyl N-oxides (210a) and (220b) with acetic anhydride and the known⁶⁷ formation of chloromethyl derivatives with chlorinating agents, it might have been expected that the dimethyl N-oxides (220a-b) would undergo

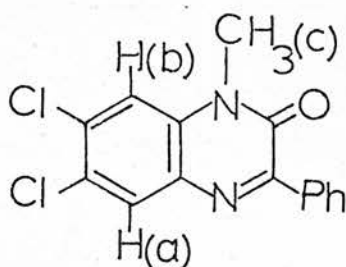
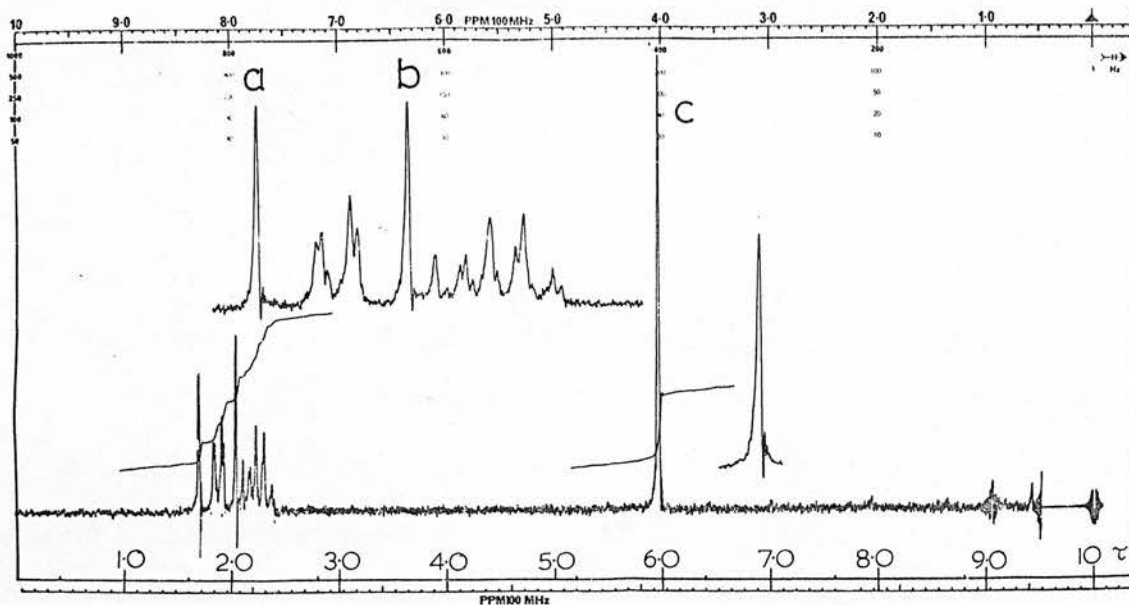


Figure 28.

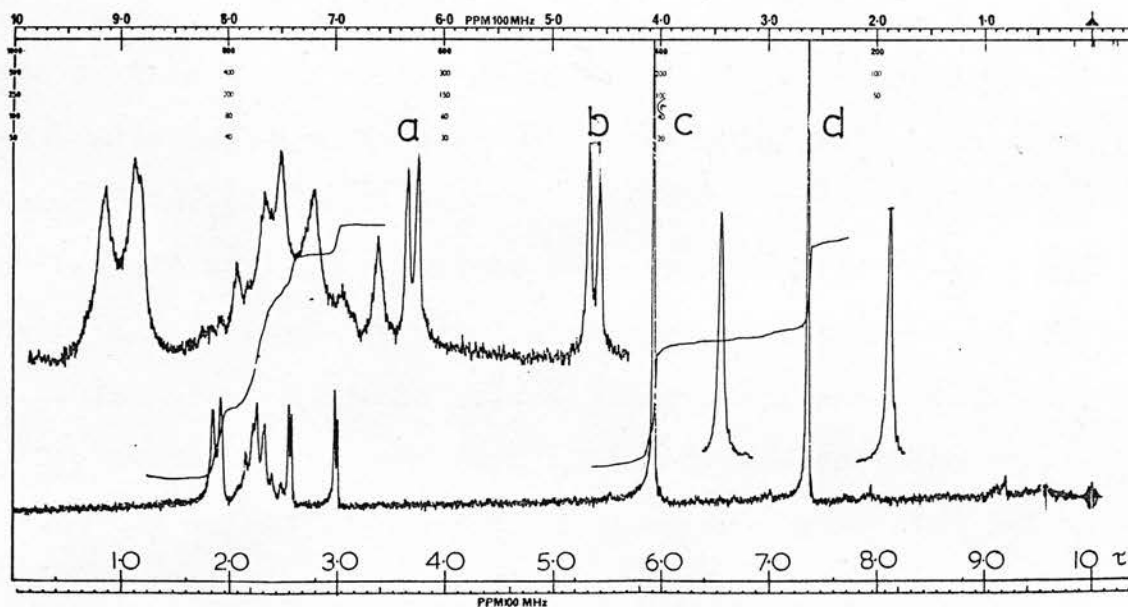


Figure 29.

¹H n.m.r. spectra of compounds (239e) (Figure 28) and (243b) (Figure 29) in trifluoroacetic acid at 100 MHz; inset expansions to 250 MHz.

chlorination of the 6-methyl group. However the ^1H n.m.r. spectra of the products lacked a methylene signal in the region of τ 4.0-5.0. Integration of the spectra indicated the presence of only six aromatic protons, one of which appeared as a singlet. This, together with elemental analysis, suggested that the products were 5- or 8-chloro-6,7-dimethylquinoxalin-3(4H)-ones. The two products were related by methylation and on the basis of previous results and the possible mechanism (see later) of the reaction, the products are formulated as the 8-chloro derivatives (240).

In contrast to the sole substitution at C(6) by the acetoxy group in the nitro-N-oxide (216f), both of the N-oxides (215f) and (216f) gave a mixture of monochloro-derivatives. Methylation of the isomer mixture obtained by reaction of the N-oxide (215f) with acetyl chloride, afforded the same mixture obtained from the N-methyl-N-oxide (216f) and acetyl chloride, but in different proportions. Although these mixtures could not be separated by fractional crystallisation or by column chromatography, their composition was established by analysis of their ^1H n.m.r. spectra (Table 5). First-order analysis of the splitting pattern established the presence in both cases of a 6,7-disubstituted compound formulated as (238f) and (239f) and a 7,8-disubstituted compound formulated as (241a-b). Reaction of the N-methyl N-oxide (216f) favoured substitution at C(6) whereas the 8-chloro isomer (241a) was the predominant product obtained from the N-oxide (215f).

Thus substituents at the 7-position have little effect

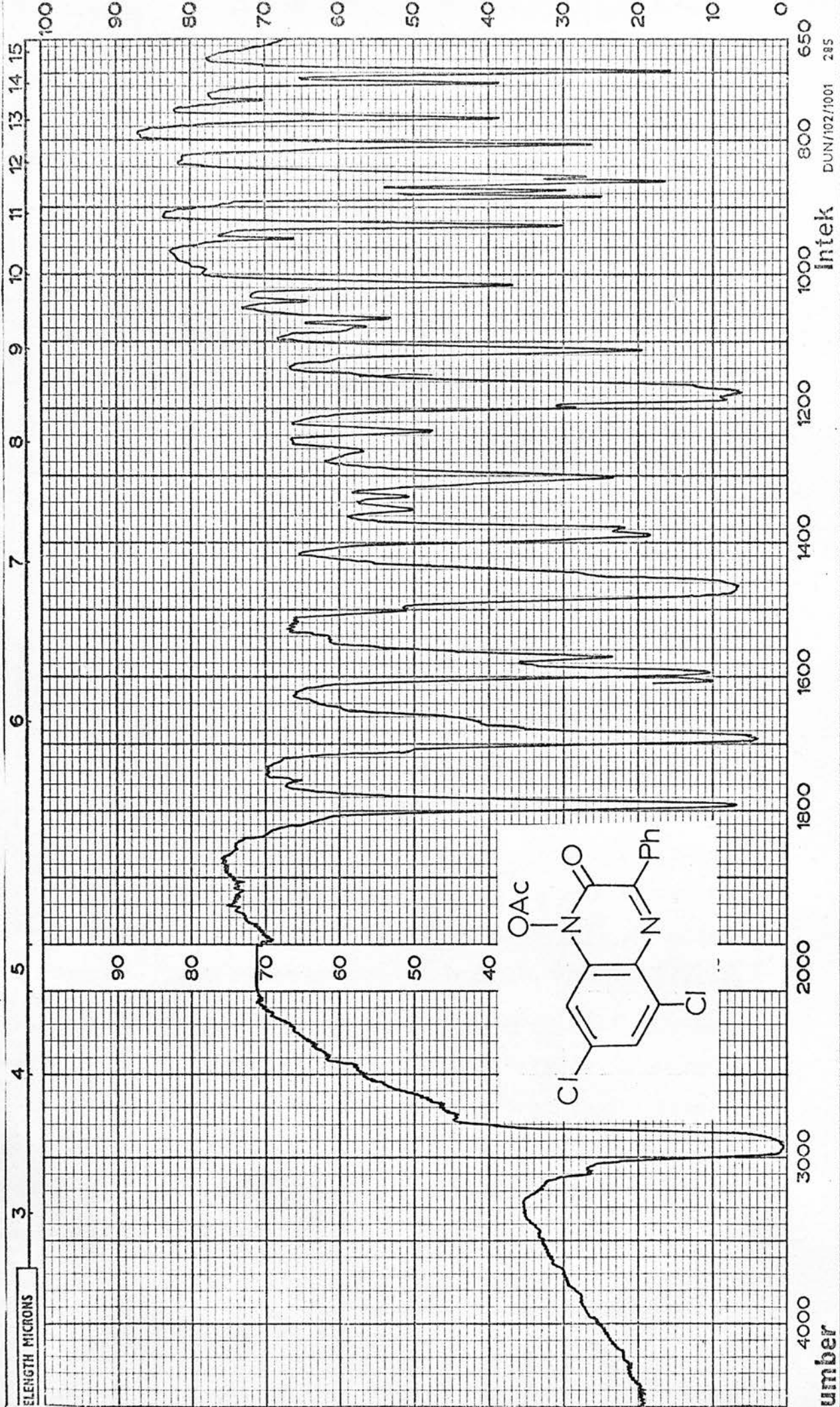


Figure 30.

on the chlorination of quinoxalin-3(4H)-one 1-N-oxides except in the case of a strongly electron-withdrawing group, such as nitro whose directing influence causes the formation of 8-substituted products in addition to the normal 6-substitution. However, even in this exceptional instance there was, as expected, no trace of substitution at the 5-position. When the 6-position is blocked with a methyl group substitution again occurs at the 8-position instead of affording a chloromethyl derivative. Attempted reaction of 2-cyano-4-methylquinoxalin-3(4H)-one 1-N-oxide (193d) with acetyl chloride afforded only unchanged starting N-oxide, showing the much greater resistance of the 2-cyano N-oxides to this type of substitution reaction.

The cyclic hydroxamic acid (202a) on reaction with acetyl chloride formed a chlorine-containing compound which showed a characteristic i.r. band at 1790 cm^{-1} (cyclic: N·OAc). Catalytic hydrogenation afforded a compound identical with the product of reduction of the chloro-hydroxamic acid (202e) and identical with the product of the reaction of the N-oxide (215a) with acetyl chloride [i.e. the 6-chloro-compound (204e)]. Consequently the chlorination product is assigned the 4-acetoxy-6-chloro-structure (242a).

On reaction with acetyl chloride, the monosubstituted cyclic hydroxamic acids (202b-e) all afforded products with characteristic bands at $1795\text{-}1785\text{ cm}^{-1}$ (cyclic: N·OAc) (see Figure 30) whose analyses corresponded to the introduction of one chlorine atom and the loss of the N-oxide group. The ^1H n.m.r. spectra of these compounds (Table 6) were in accord

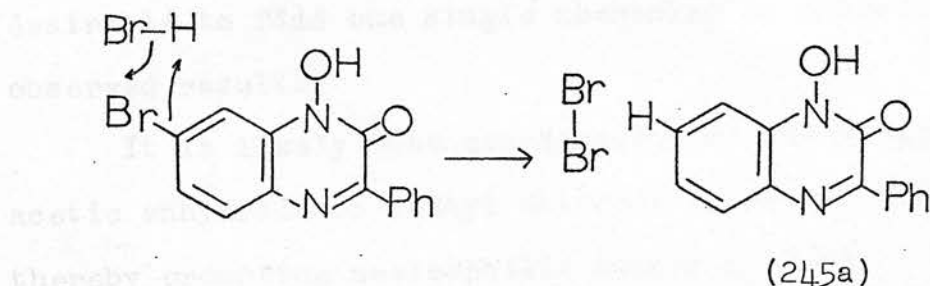
with the 6,8-disubstituted structures (243), because of the presence of two meta-coupled protons in the aromatic region (see Figure 29). It is again noticeable that in the 6-methyl derivative (202b), chlorination is directed into the 8-position rather than into the methyl group itself.

The reaction of the dimethyl hydroxamic acid (210a) with acetyl chloride appears to fall into a different category. On the basis of mass spectral and analytical evidence the product appears to be a dichloro-derivative of the deacetylated quinoxalone (211a). Because of the insolubility of this product it was not possible to obtain a ^1H n.m.r. spectrum which would clearly show whether this product was a mixture of dichloro-isomers or a single compound. By the same token it was not possible to distinguish between a chloromethyl product and a ring-substituted product. However, as no other methyl compound has shown itself susceptible to chlorination in the methyl group, this product is tentatively assigned the 5,8-dichloro structure (244). Further support for this structure stems from the fact that this is the only example found in which the N(4)-oxygen function is lost during the course of the reaction. This suggests involvement of the N(4)-oxygen function and thus the most likely site of substitution is C(5). This result in no way parallels the substitution at the 5-position found by Suschitzky¹⁶¹ because in that case the substrate (225) studied contains no N(4)-oxygen function.

Ahmad¹³⁸ reported that when 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215a) was heated with fuming hydrobromic acid

the deoxygenated, halogen-free base (204a) was obtained. This result is not entirely unexpected because of the powerful reducing properties of hydrobromic acid. Despite the fact that a mixture of acetyl bromide and acetic acid functions effectively as a mixture of acetic anhydride and hydrogen bromide, it was decided by analogy with the acetyl chloride-acetic acid reactions to attempt to effect nucleophilic bromination using this reaction medium. The reaction of 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215a) with fresh acetyl bromide did not give the 6-bromo-derivative (204d) but resulted solely in reduction of the N-oxide (215a) to the deoxygenated, halogen-free base (204a). Reaction of the same N-oxide (215a) with old (red) acetyl bromide did give a product containing bromine which, however, proved to be simply the hydrobromide of the deoxygenated base (204a). That the red colour of the old acetyl bromide was due presumably to hydrogen bromide and not to free bromine was shown by the failure of the acetyl bromide to react with phenol to form 2,4,6-tribromophenol. Failure to undergo bromination is not restricted to the N-oxide (215a). The corresponding N-methyl-N-oxide (216a) was also reduced to the parent base (218a) without bromination. Likewise the dimethyl N-oxide (220b) also reacted in this manner to afford (211b) without bromination of the ring or of the 6-methyl group. The significance of these reactions is that reduction must be fast in comparison to bromination. This fact also lends support to the nucleophilic nature of the substitution reaction.

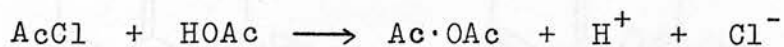
The cyclic hydroxamic acids (202), however reacted slightly differently with acetyl bromide. Although bromination was not found to occur the reduction process proved to be more specific. In contrast to the reaction of the cyclic hydroxamic acids (202) with sodium dithionite wherein both oxygen functions on nitrogen were reduced, in this case the N(4)-hydroxyl group proved resistant to reduction. Treatment of the unsubstituted cyclic hydroxamic acid (202a) with acetyl bromide in acetic acid thus afforded the N-hydroxy compound (245a) which still gave a deep red colour with iron (III) chloride in ethanol. Similarly the chloro-compound (202e) was specifically reduced to the hydroxamic acid (245b) whose structure was proved by its conversion in acetic anhydride into the compound (242a) which was also obtained by the reaction of acetyl chloride with the unsubstituted hydroxamic acid (202a). This result is also further evidence for the orientation of the chloro-hydroxamic acid (202e). In order to exclude the possibility that the compound (245a) was formed by bromination and subsequent debromination, the



hydroxamic acid (202d) was treated with acetyl bromide in acetic acid. The product (242b) still contained halogen thus discounting the possibility of debromination. However

this reaction differed from the previous examples as the product isolated was the N-acetoxy derivative (242b). Although proof is lacking, proposals^{137,141} have been put forward regarding the possible mechanism of chlorination and acetylation of the benzene nucleus in quinoxaline N-oxides. The various mechanistic pathways possible are thus considered at this stage in the light of the results obtained.

Although acetic anhydride is thought to react in an ionic manner, it is known that acetoxy or acetyl radicals are generated to some extent. However acetyl chloride as a reaction medium is known to ionise and thus in the presence of acetic acid can be considered as a source of chloride ion.



Also, the substitution pattern (6- and 8-positions, or 6-methyl group) was not random, and was that expected for specific nucleophilic attack. Thus the possibility of a radical mechanism is unlikely. Several mechanisms involving nucleophilic attack can be invoked but it would be ideally desirable to find one single mechanism to embrace all of the observed results.

It is likely that coordination of the N-oxide group by acetic anhydride or acetyl chloride occurs initially thereby promoting nucleophilic attack at C(6). Certain benzimidazole N-oxides are known to undergo nucleophilic substitution in the benzene ring in the presence of coordinating agents.¹⁴⁴ Consequently attempts were made to react the quinoxaline N-oxide (216a) with nucleophiles, in

the presence of coordinating agents to see if substitution would occur. When stirred with potassium cyanide in the presence of benzoyl chloride the N-oxide (216a) was recovered unchanged, and on heating under reflux with potassium cyanide in acetic anhydride as solvent, decomposition to an intractable oil occurred. Ethyl cyanoacetate, in the presence of acetic anhydride, also failed to react with the N-oxide (216a).

As these attempts were unsuccessful it was decided to preform a coordinated species, namely the boron trifluoride adduct (249) of the N-oxide (216a) and to attempt its reactions with nucleophiles.



(249)



(250)

The adduct (249) had to be used in a crude form as it was unstable to crystallisation, reverting to the N-oxide (216a). However it was recovered unchanged, together with some of the N-oxide (216a), on attempted reaction with ethyl cyanoacetate.

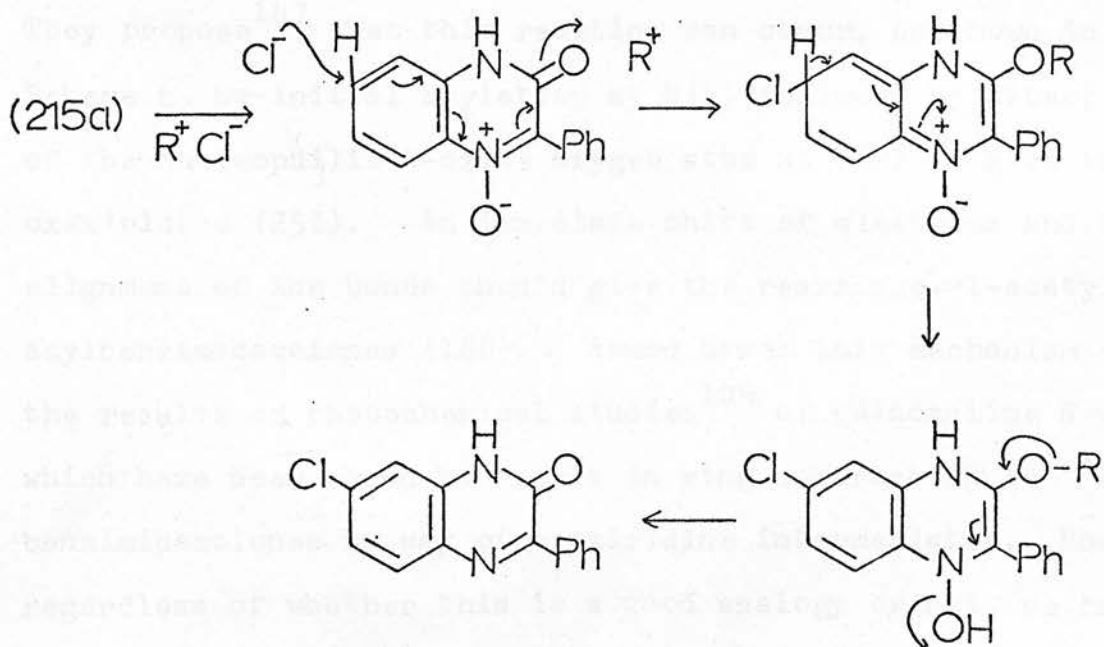
There are very many examples known of the coordination of N-oxides with acetic anhydride to form N-acetoxonium salts.¹⁶¹ As an N-acetoxonium salt is a possible intermediate in the substitution reactions described above, an attempt was made to prepare the acetoxonium perchlorate (250) and to react it with acetate ion and chloride ion in the form of their lithium salts. Treatment of the N-oxide (216a) with acetic anhydride

and perchloric acid afforded a yellow solid which decomposed on standing. This is presumably the desired perchlorate (250) but attempts to reconvert it into the N-oxide (216a) by treating it with dilute ammonium hydroxide yielded only the 6-hydroxyquinoxalone (227a). The perchlorate was reacted with lithium acetate and lithium chloride but in both cases yielded only the 6-hydroxy compound (227a) and the N-oxide (216a) instead of the expected 6-acetoxy compound (226a) and the 6-chloro compound (239a).

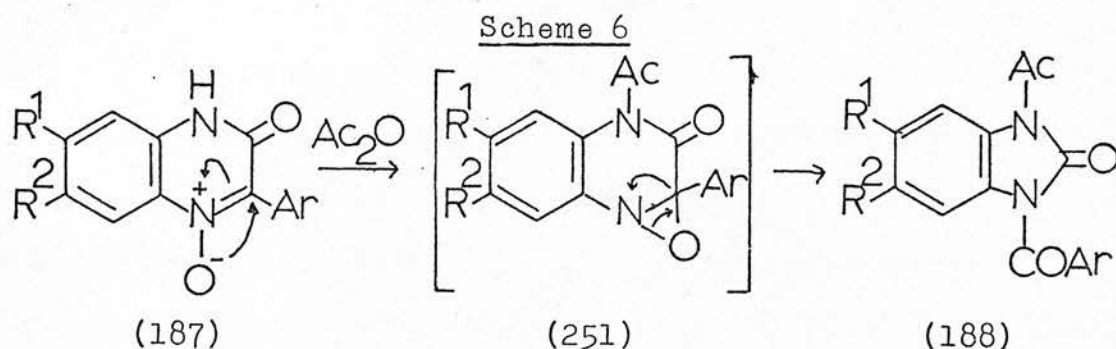
Therefore these latter experiments failed to provide convincing evidence for, or against, any type of nucleophilic reaction mechanism.

Ahmad and his coworkers¹³⁷ have proposed a mechanism for the chlorination reaction (Scheme 5), which they assume¹⁴⁷ is also applicable to the introduction of an acetoxy group.

Scheme 5

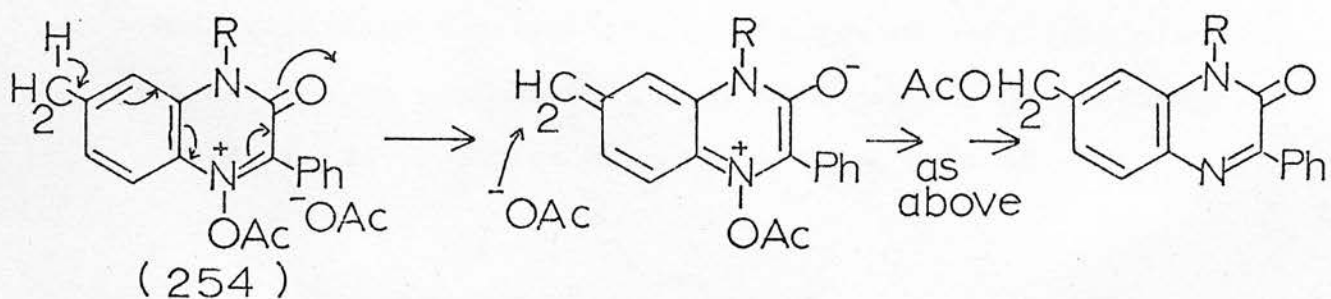
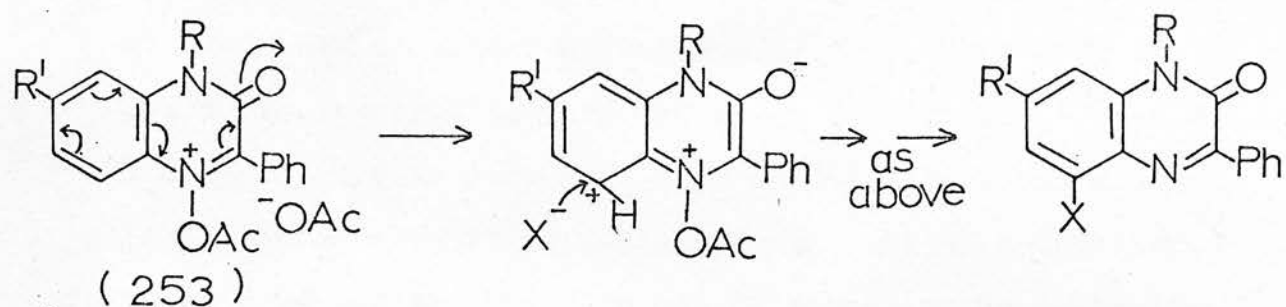
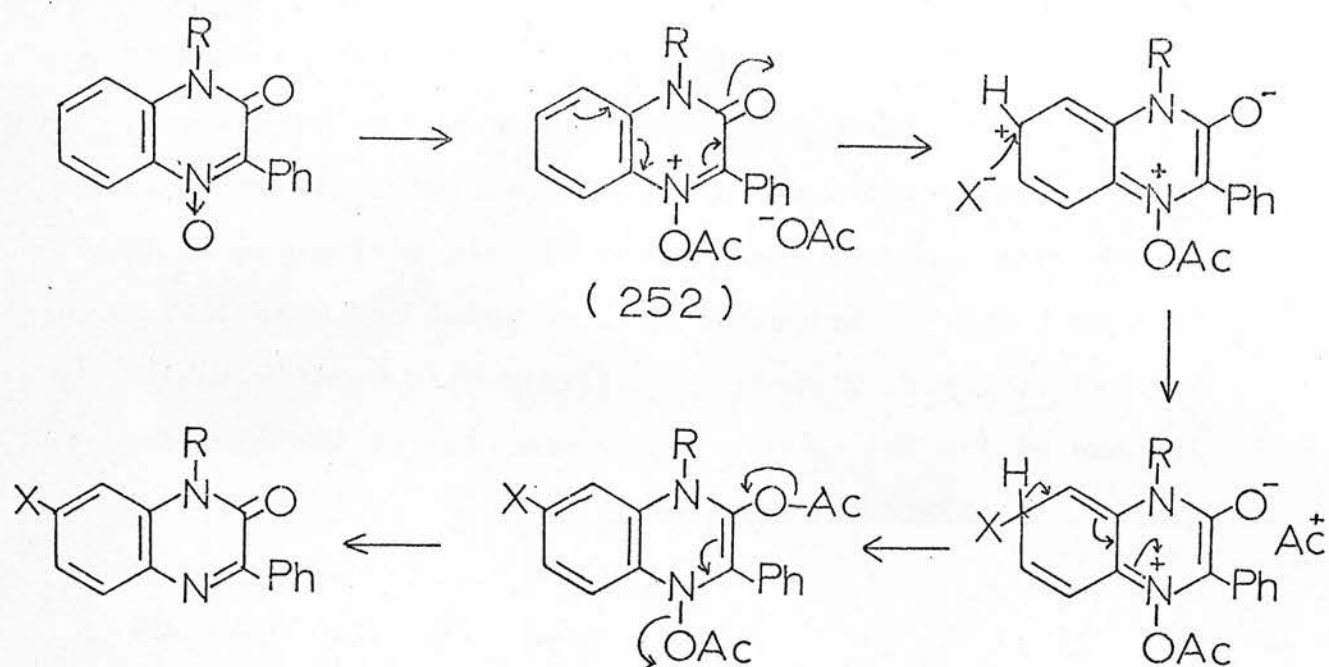


They assume that the reagent attacks the oxygen function at C(3), probably augmented by protonation of the N-oxide group, directing nucleophilic attack into the 6-position as shown. This mechanism accounts for the formation of the observed chlorinated products but presumes that the acylating agent attacks the carbonyl function at C(3) in preference to the N-oxide group. It is pertinent to point out here that Ahmad and his coworkers propose an entirely different mechanism (Scheme 6) for the novel ring contraction of the N-oxides (187) to benzimidazolones (188).



They propose¹⁴⁷ that this reaction can occur, as shown in Scheme 6, by initial acylation at N(4) followed by attack of the nucleophilic N-oxide oxygen atom at C(2) to give the oxaziridine (251). An immediate shift of electrons and re-alignment of the bonds should give the rearranged 1-acetyl-3-acylbenzimidazolones (188). Ahmad bases this mechanism on the results of photochemical studies¹⁰⁹ of quinoxaline N-oxides which have been shown to result in ring contraction to benzimidazolones by way of oxaziridine intermediates. However, regardless of whether this is a good analogy or not, we have shown (see Section 3) that the quinoxalone (271a) does not

Scheme 7.



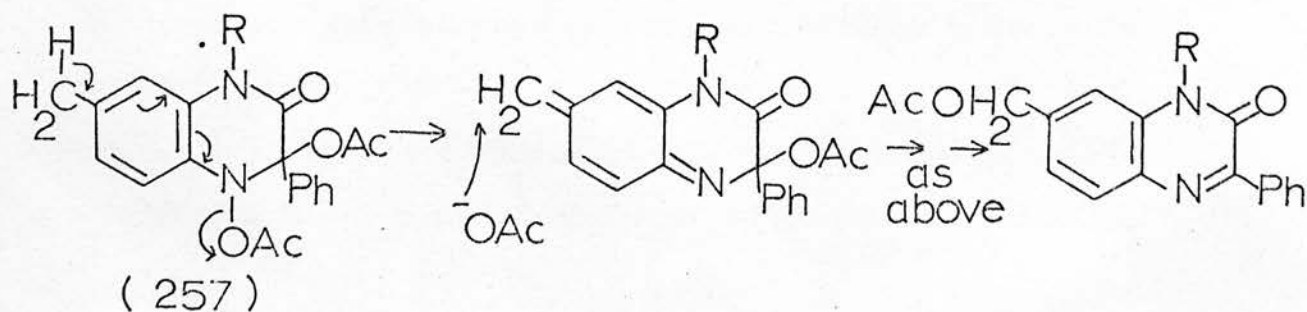
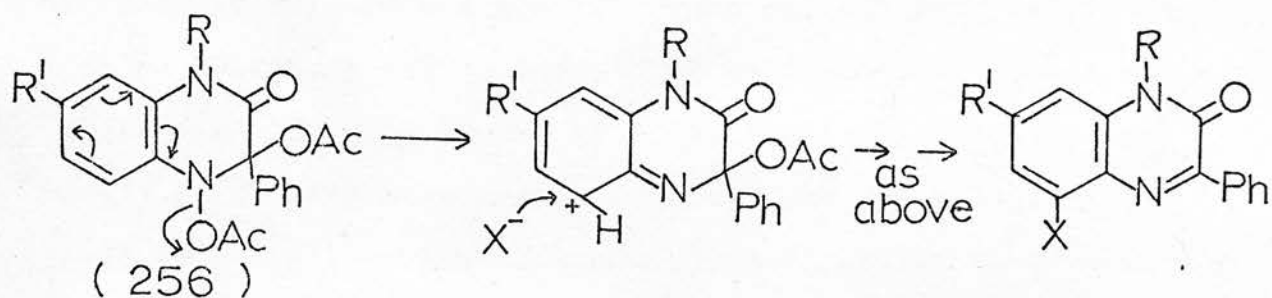
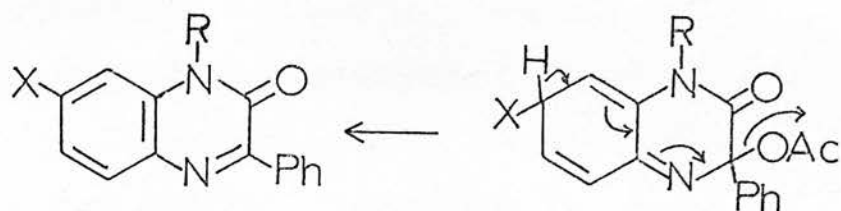
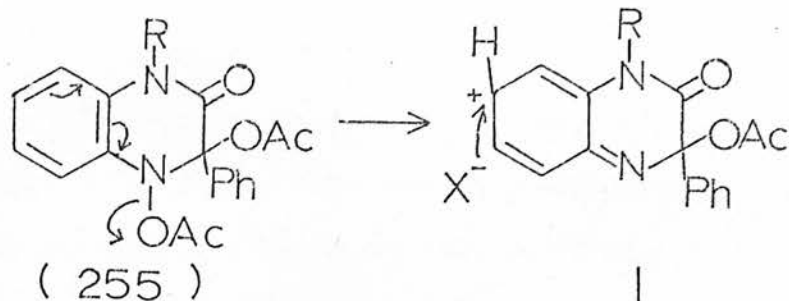
undergo acetylation at N(4) on prolonged heating with acetic anhydride and thus the first step in Scheme 6, is in question. A more basic criticism, however, is that the same molecule should react by such completely different types of mechanism, as illustrated in Schemes 5 and 6, with reagents so similar in behaviour as acetic anhydride and acetyl chloride. In addition the mechanism proposed in Scheme 6 does not explain why ring contraction should occur with the N-oxide (215a) but not with the N-methyl derivative (216a). Thus a single mechanism which could explain both types of reaction is desirable.

If one assumes that the acetoxonium salt (252) is formed initially, further attack by acetic anhydride could take place at C(6) by a mechanism (Scheme 7) similar to Ahmad's mechanism (Scheme 5) for the chlorination reaction. This mechanism can also account for the formation of 8-substituted products, as shown for the acetoxonium salt (253) in which the 6-position is blocked. The formation of acetoxymethyl derivatives is in accord with this mechanism as indicated for the 6-methyl acetoxonium salt (254). However it is difficult to see why the adduct (252; R=H) should undergo preferential ring contraction when reacted further with acetic anhydride.

It has been shown by Ahmad and his coworkers^{137,138,147} that neither substitution in the benzene ring nor ring contraction occurs in the absence of a C(3) oxygen function. It has been assumed up to this point, that the C(3) oxygen function is involved, as shown in Schemes 5 and 7 in the

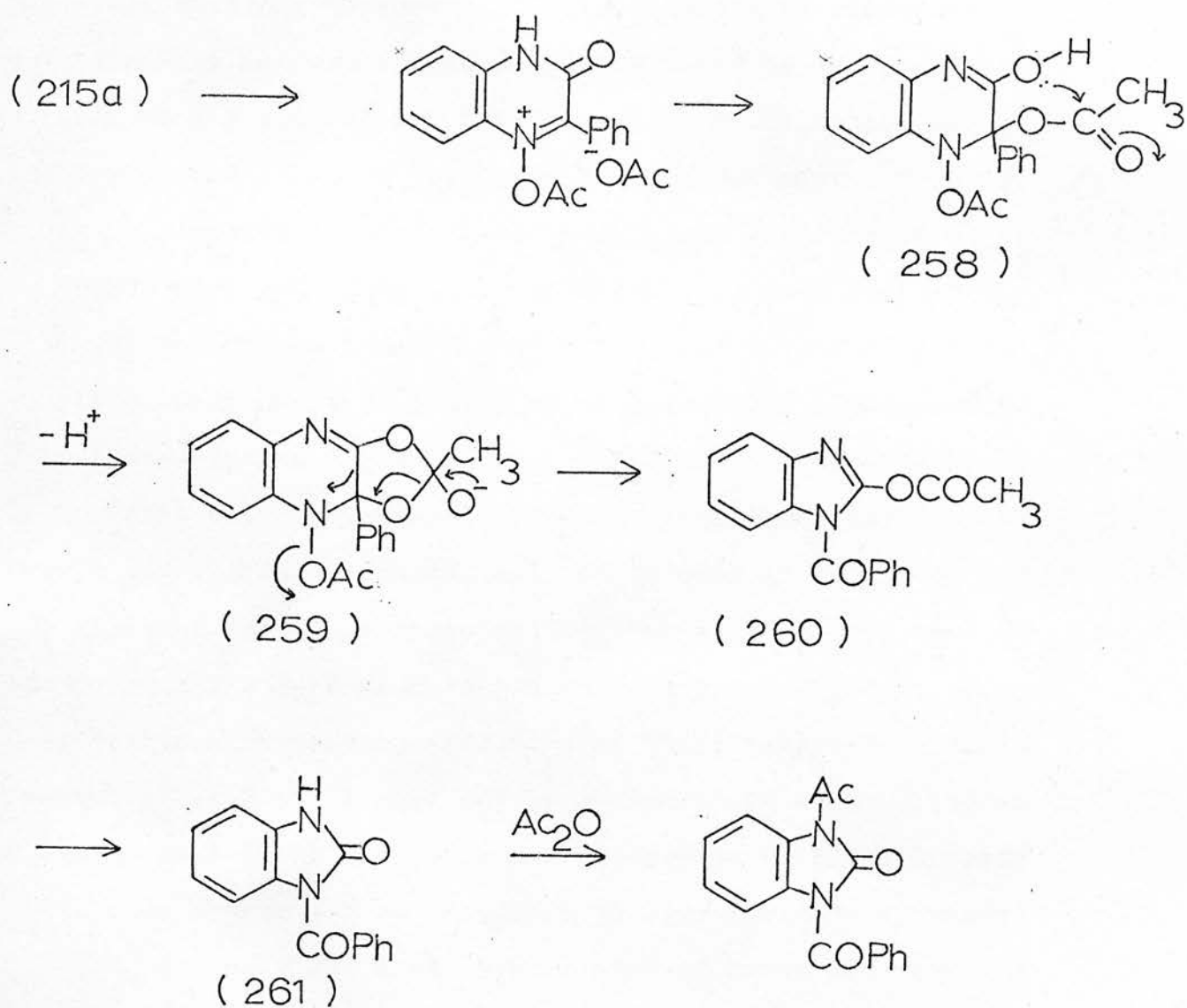
Scheme 8

(252)



electron shifts necessary for reaction to occur. However, the presence of the C(3) oxygen function could be vital in a different way. Many N-oxides are known to form Riessert-type adducts by addition of a reagent to the N-oxide group and at C(2) to give structures of the type (255). The carbonyl function at C(3) effectively dearomatises the heterocyclic ring thus making this type of addition easier. The formation of the substituted products can be accounted for by the mechanism shown in Scheme 8, which does not involve the C(3) oxygen function at any later stage. However, this could account for the lack of reactivity of aromatic quinoxaline N-oxides, which probably could not form the initial adduct of the type (255). The formation of the 8-substituted products can be explained as shown (Scheme 8) for 6-substituted adducts (256). Similarly 6-acetoxymethyl derivatives could arise from the 6-methyl adducts (257). The strongest feature of this mechanism is that it can also account for the ring-contraction reaction. The N-oxides (215) possessing a free hydrogen atom at N(4) differ from the 4-methyl N-oxides (216) in that they possess an enolisable centre. Thus if an adduct of the type (255; R=H) is formed then it could be written in the enol form (258) (see Scheme 9). Attack by the lone pair of electrons on the oxygen atom of the hydroxyl group in this intermediate (258) on the neighbouring acetoxyl group at C(2), as shown in Scheme 9, would give the intermediate (259). This could then break down with concomitant 1,2-bond shift to afford the acetoxybenzimidazole derivative (260). This unstable molecule could

Scheme 9.



then afford the required N-acetyl benzimidazolone in a stepwise manner as shown or by a rearrangement involving migration of an acetyl group from oxygen to nitrogen. This ring contraction process would also be possible for the N-hydroxy N-oxides (202) but for the fact that preliminary acetylation occurs at the N-hydroxyl group.

By consideration of this mechanism, there must be two competing attacks, one giving rise to a product substituted in the benzene ring and the other to a ring-contracted product. Thus attack at the benzene ring with acetate ion must be a faster process than the alternative ring contraction except in the case of the N-oxides (215) which possess a possible participating group. The fact that no ring contraction occurs with the N-oxides (215) in reaction with acetyl chloride can be explained by the fact that chloride ion is a stronger nucleophile than acetate ion and thus even allowing for participation, nucleophilic attack at the benzene ring is the faster reaction.

However, it must be emphasised that there is no evidence to back up this argument and until further evidence is available, details of mechanism must remain speculative.

SECTION THREE

SOME 1,3-DIPOLAR CYCLOADDITION REACTIONS OF
QUINOXALIN-3(4H)-ONE 1-N-OXIDES

SOME 1,3-DIPOLAR CYCLOADDITION REACTIONS OF QUINOXALIN-3(LH)-
ONE 1-N-OXIDES

In recent years, the concept of 1,3-dipolar cycloaddition has been developed, in the main by Huisgen.^{99,164} Although numerous individual examples of this type of reaction were previously known, Huisgen extended its use to include a series of 1,3-dipolar systems, many of which were previously unknown. The importance of this type of cycloaddition reaction is in its utility for the synthesis of a remarkably wide range of five-membered heterocycles.

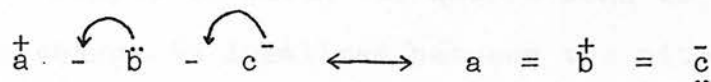
A cycloaddition of the type, $3 + 2 \rightarrow 5$, leading to an uncharged five-membered ring cannot occur with octet-stabilised reactants possessing no formal charges. A 1,3-dipole a b c must be defined such that atom a possesses an electron sextet (i.e. an incomplete valence shell combined with a positive formal charge), and atom c, the negatively charged centre has an unshared electron pair. The combination of such a 1,3-dipole with a multiple bond system d e (the dipolarophile) is termed a 1,3-dipolar cycloaddition.



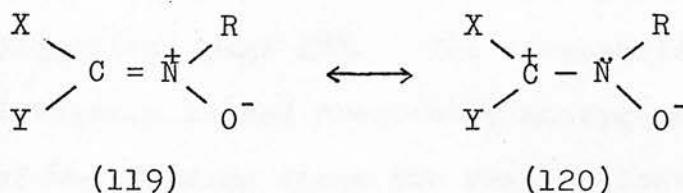
1,3-Dipolar cycloaddition fits into a regular sequence between olefin dimerisation and Diels-Alder synthesis.

Compounds containing an electron sextet at a carbon, nitrogen or oxygen atom are not stable so the foregoing description of a 1,3-dipole can only signify one of the

dipole's resonance structures. Stabilisation can be achieved if an unshared pair of electrons at atom b can relieve the electron deficiency of a by forming an additional bond



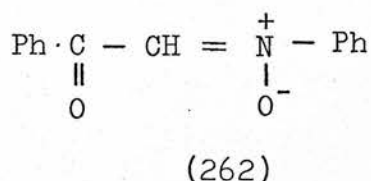
Thus b is now positively charged and all centres have completely filled valence shells. Such 1,3-dipoles are said to have internal octet stabilisation. Systems which fall into this category in which a = Carbon, b = Nitrogen, and c = Oxygen, are the azomethine N-oxides (nitrones)^{165,166} which exhibit the mesomeric effect (119) \longleftrightarrow (120).



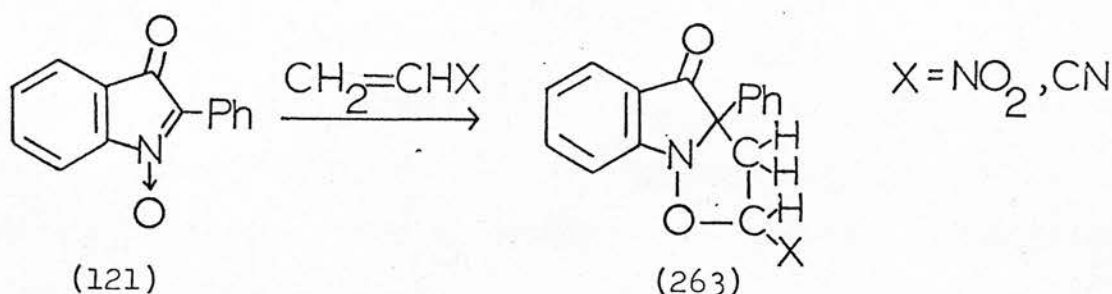
Colonna⁹ was the first to demonstrate the similarity, in some of their reactions, of heterocyclic N-oxides to nitrones. This similarity may be attributed to the similar mesomeric effects in the N-oxide and nitrone structures (see above). Thus, in a general sense, heterocyclic N-oxides can be regarded as cyclic nitrones. It is well known that nitrones undergo 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles.^{99,166} Whilst bearing in mind that the mere presence of the azomethine N-oxide group ($>\text{C}=\overset{+}{\text{N}}-\bar{\text{O}}$) in a molecule does not necessarily endow it with nitrone characteristics, it is a reasonable supposition that some heterocyclic N-oxides at least, will undergo 1,3-dipolar cycloaddition reactions.

The polarisation of the nitron group is controlled by the electronic effects of the groups X, Y and R. At the one extreme is the system represented by the structure (119; X, Y, and R = alkyl) in which the double bond is fixed and the positive charge is localised between the nitrogen and the carbon atoms of the azomethine system. At the other extreme is pyridine 1-N-oxide in which a high degree of delocalisation results from the aromatic character of the ring. In between these extremes all degrees of delocalisation can exist. Several instances are known in which heteroaromatic N-oxides react with dipolarophiles. Thus, pyridine 1-N-oxide reacts with phenyl isocyanate to form 2-(N-phenylamino)pyridine (123) (see Introduction, page 28). The isoxazolidine ring in the adducts initially formed frequently undergoes ring-opening because of the driving force for rearomatisation. The end result in such cycloadditions appears to be nucleophilic substitution, accompanied by deoxygenation of the N-oxide group. Relatively few examples of this type of reaction are known for heteroaromatic N-oxides. In such molecules the similarity to the nitron system is much less marked due to the delocalisation of the positive charge into the aromatic ring. This effect is readily illustrated by the fact that 3,4-dihydroisoquinoline 2-N-oxide (264) undergoes 1,3-dipolar cycloaddition 40,000 times faster than the corresponding fully aromatic N-oxide. It also follows that when X or Y [see (119)] is electron-attracting the electron density on the carbon atom is decreased thus enhancing its electrophilic properties. This situation is found in

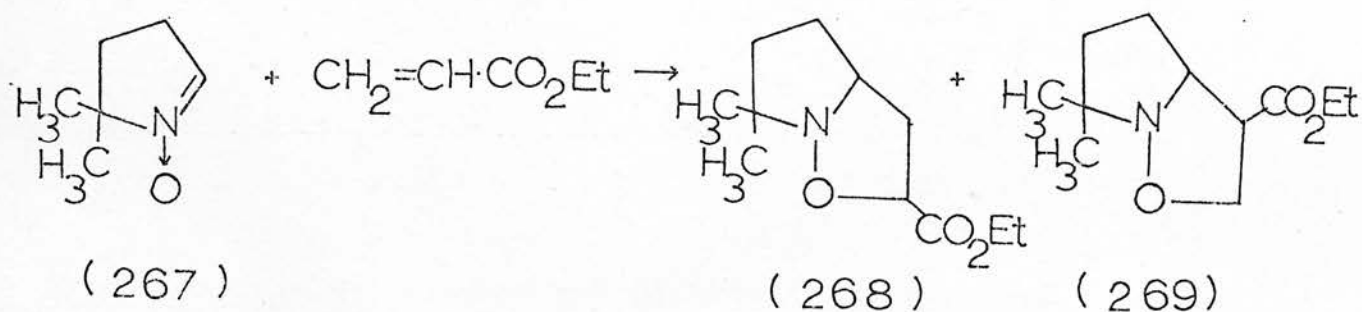
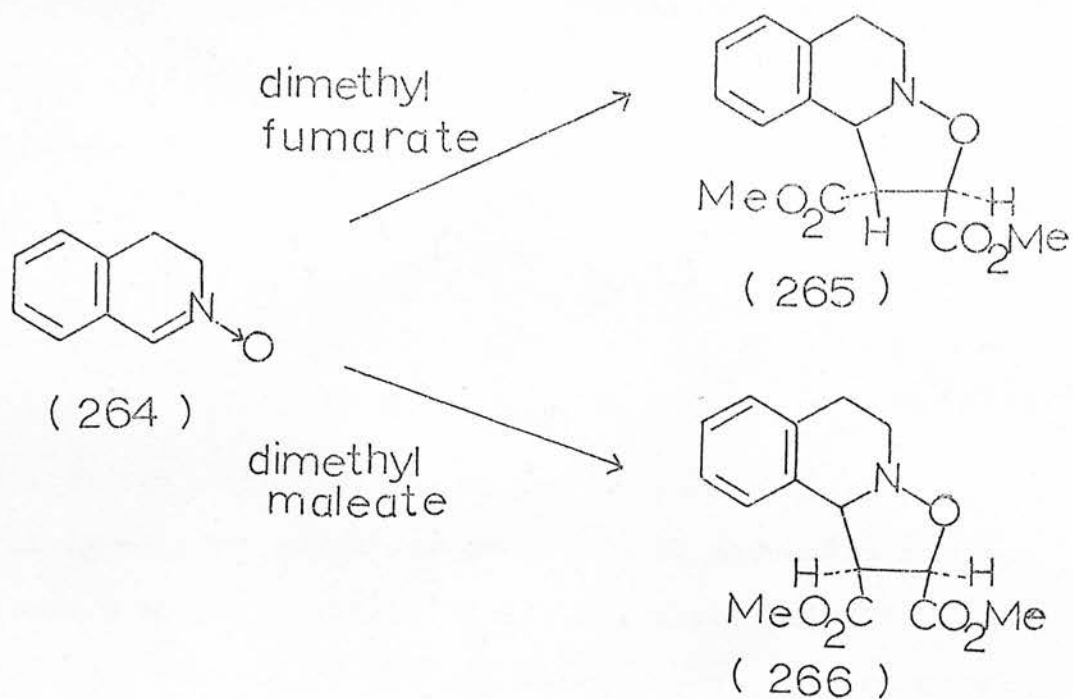
C-benzoyl-N-phenylnitrone (262) which reacts 110 times faster in 1,3-dipolar cycloadditions than the corresponding C,N-diphenylnitrone.⁹⁹



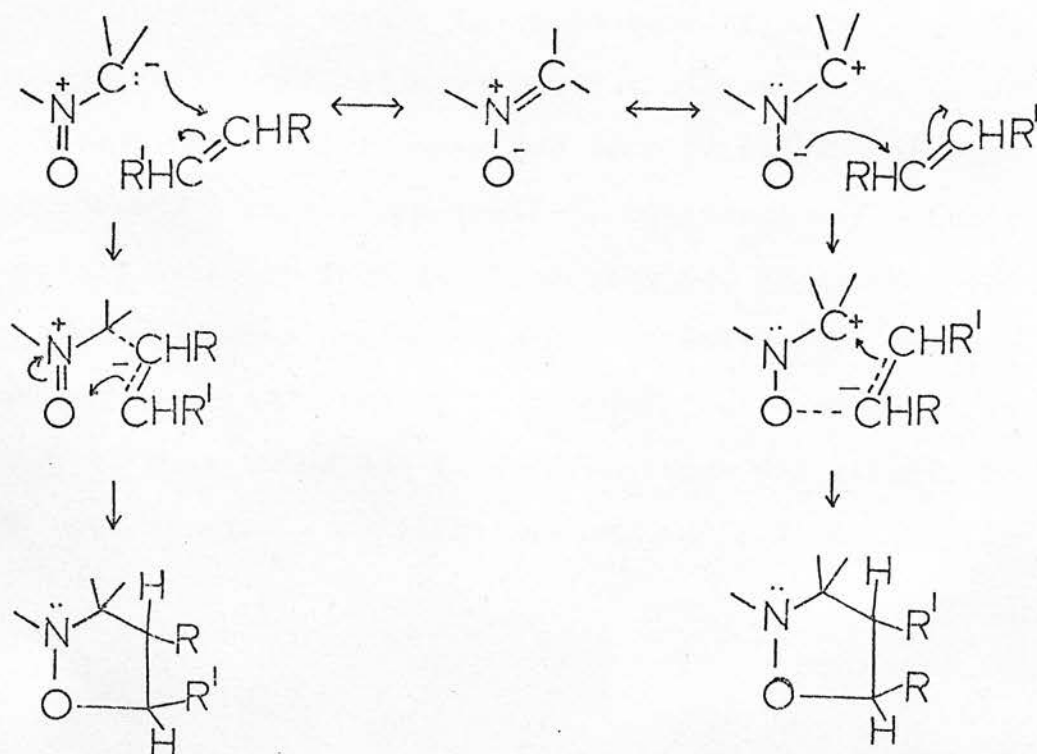
Isatogens can be considered to be the cyclic analogues of nitrones such as (262) and are known to undergo 1,3-dipolar cycloaddition reactions fairly readily. Thus 2-phenylisatogen (121) reacts with dipolarophiles such as nitroethylene and acrylonitrile to form cycloadducts (263).¹⁶⁷



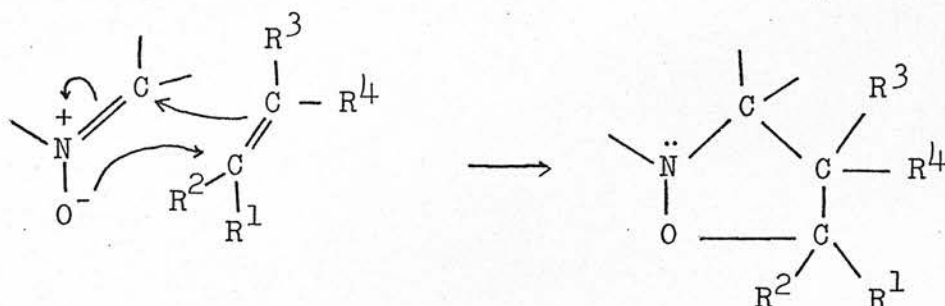
An important factor in the preparative application of 1,3-dipolar cycloaddition is the reactivity of the dipolarophile. Phenyl isocyanate and carbon disulphide have been shown to be excellent dipolarophiles, demonstrating that this type of reactivity does not necessarily match that found for dienophiles in the Diels-Alder additions. The strength of the σ -bonds in the adducts is another decisive factor. However, this cannot be predicted and each 1,3- system must be considered individually. In most cases the mechanism of 1,3-dipolar cycloaddition is not known with certainty. Neither is it clear whether addition always follows the same



Scheme 10.

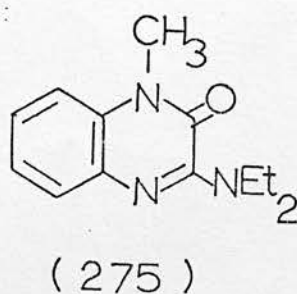
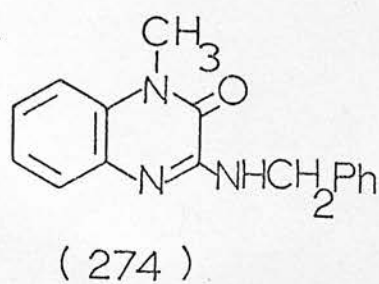
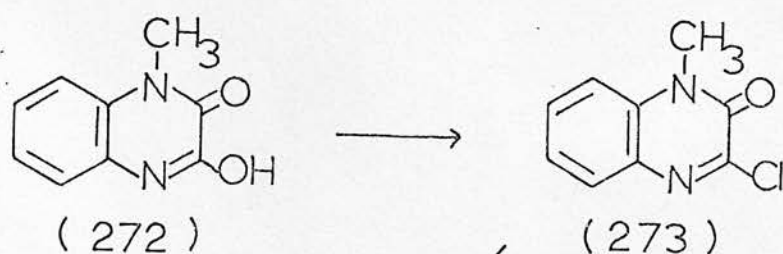
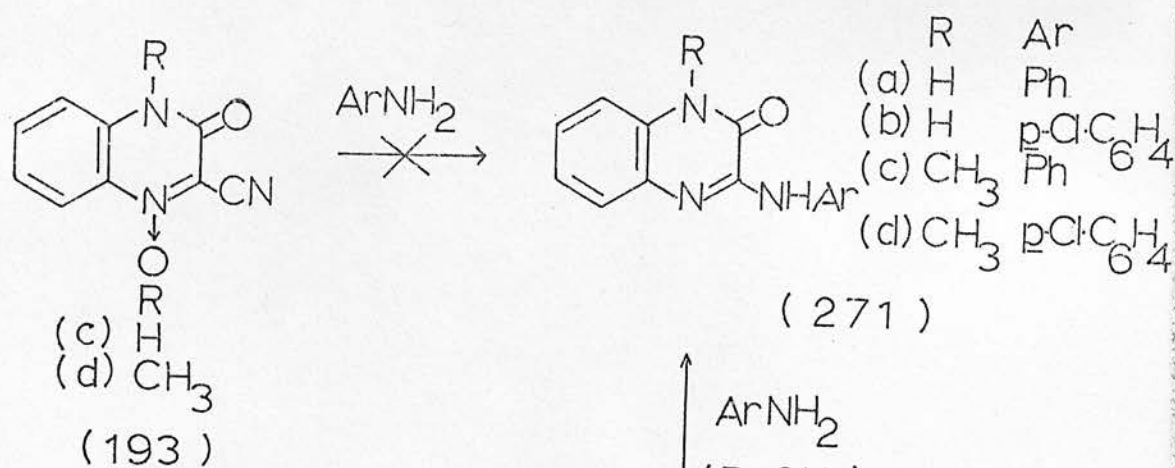
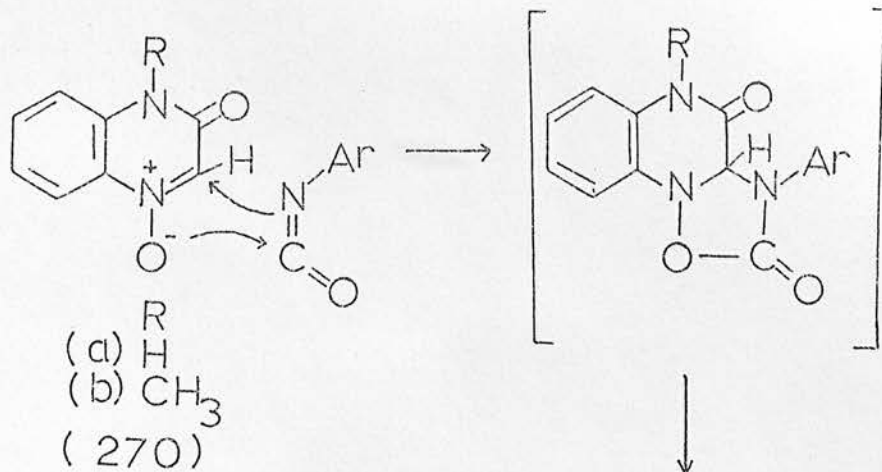


pathway. There are basically two possibilities to be considered. Firstly, a concerted one-step process - e.g.



Secondly, a step-wise process (Scheme 10) in which the structure of the intermediate depends on the polarisability of the reagents. The former mode of addition, which is necessarily stereospecifically cis-, is favoured by Huisgen¹⁶⁴ who demonstrated predominant cis- addition in the systems which he studied. Thus reaction of 3,4-dihydro-isoquinoline 2-N-oxide (264) with dimethyl fumarate and dimethyl maleate afforded respectively the diastereoisomers (265) and (266). The stepwise process is favoured by Delpierre and Lamchen¹⁶⁶ on the basis of their studies of the cycloaddition of ethyl acrylate to 1-pyrroline 1-N-oxides.¹⁶⁸ A similar step-wise mechanism is suggested for the formation of the isomeric isoxazolidines (268) and (269) from 5,5-dimethylpyrroline 1-N-oxide (267).¹⁶⁹

1,3-Dipolar cycloaddition reactions of benzimidazole N-oxides have been thoroughly investigated by Kano and Takahashi¹⁰² but no such studies have been undertaken in the quinoxaline series. Quinoxalin-3(4H)-one 1-N-oxides (270a-b) exist in the cyclic amide forms and thus bear a structural similarity to isatogens such as 2-phenylisatogen (121). Hence this particular type of quinoxaline N-oxide is



potentially reactive from the point of view of 1,3-dipolar cycloaddition, particularly in the case of the N-methyl N-oxide (270b) which is unable to tautomerise to an aromatic form.

When the N-oxide (270a) was heated under reflux in dry xylene with phenyl isocyanate the N-oxide (270a) was recovered unchanged because of its insolubility. Heating in dimethylformamide, however, gave an almost quantitative yield of a product whose molecular weight and analysis were in accord with the addition of the elements of phenyl isocyanate to the N-oxide (270a), and subsequent loss of carbon dioxide. By analogy with the reaction of pyridine 1-oxide with phenyl isocyanate (see Introduction, page 28), and the presence of an absorption band at 3300 cm^{-1} in the i.r. spectrum of the product, it was thought likely that the product had the structure (271a). The N-oxide (270b) on heating with phenyl isocyanate in dry xylene similarly afforded a product formulated as the N-methyl analogue (271c). In both of these reactions (using dry solvents) the use of a 10% excess of phenyl isocyanate afforded higher yields of the products than if an equivalent amount of phenyl isocyanate is used. Presumably some of the phenyl isocyanate is lost by conversion into diphenylurea by moisture in the atmosphere. Attempts to methylate the product derived from the N-oxide (270a), in order to establish the relationship with the product derived from the N-oxide (270b) were unsuccessful. In an attempt to establish the presence of an NH-group both products were heated with acetic anhydride

but failed to yield acetyl derivatives.

Ahmad¹⁷⁰ has reported that heating 2-cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) with aniline gives a product formulated as (271a). The m.p.s of Ahmad's compound (248°) and that of the product derived from the reaction of the N-oxide (270a) with phenyl isocyanate, (252°), are very similar. Consequently the reaction of the cyano-N-oxide (193c) with aniline was carried out in the hope of establishing unambiguously the structure of the product obtained by cyclo-addition. However, when the cyano-N-oxide (193c) was heated under reflux with excess aniline in dry xylene, the N-oxide (193c) was recovered unchanged. Elevation of the reaction temperature by heating the two reagents in dimethylformamide resulted in the formation of an intractable tar. Similar attempts to convert the N-methyl-N-oxide (193d) into the compound (271c) were also unsuccessful. Thus, heating the N-oxide (193d) in aniline also gave an intractable tar. Alternatively, when the N-oxide (193d) and aniline were heated in dry xylene, an amorphous brown solid was obtained which was not identical with the product derived from the N-oxide (270b) and phenyl isocyanate and did not possess spectral (i.r.) properties consistent with the expected structure (271c).

It had previously been shown that the 2-chloro-group in 2-chloro-4-methylquinoxalin-3(4H)-one (273) is susceptible to nucleophilic displacement by methoxide ion¹⁷¹ and by N-methylaniline.¹⁷² Application of this type of nucleophilic displacement using aniline should therefore yield

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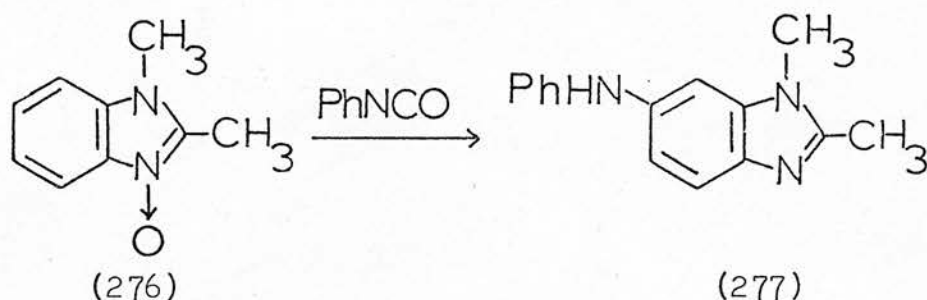
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the desired N-phenylamino-derivative (271c). When the readily available¹⁷¹ 2-chloro-4-methylquinoxalin-3(4H)-one (273) was heated with two equivalents of aniline, in dry xylene, a solid separated out, which was water soluble, and was shown by its i.r. spectrum to be aniline hydrochloride. Work-up of the reaction mixture afforded a crystalline solid in high yield, which was identical with the product of the reaction of phenyl isocyanate with the N-oxide (270b), thus confirming its structure as (271c). The product obtained from the N-oxide (270a) is assigned the N-phenylamino-structure (271a) by analogy.

To see if the dipolar reactivity of the N-oxides (270a-b) could be extended to other isocyanates the reactions of these compounds with p-chlorophenyl isocyanate and methyl isocyanate were next studied. The N-oxide (270b), on heating with p-chlorophenyl isocyanate in dry xylene, afforded a chlorine-containing compound resembling the N-phenylamino-derivative (271c) in its properties. Its structure was established as (271d) by showing it to be identical with the product obtained by heating 2-chloro-4-methylquinoxalin-3(4H)-one (273) with p-chloroaniline. In contrast, the N-oxide (270a) was recovered unchanged when it was heated with p-chlorophenyl isocyanate in dimethylformamide. The only product isolated in this reaction was identified as di-(p-chlorophenyl)urea. None of the expected product (271b) could be detected in the reaction mixture. The use of excess p-chlorophenyl isocyanate in this reaction gave the same

result. Both N-oxides (270a-b) were recovered unchanged on attempted reaction with methyl isocyanate.

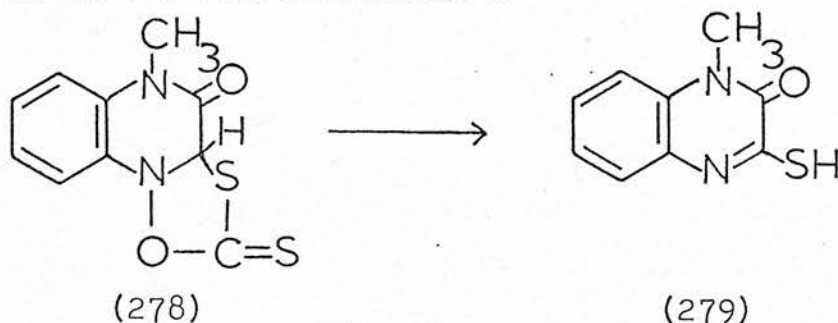
Although no intermediate isoxazolidines were isolated in the reactions of the N-oxides (270a-b) with phenyl- and *p*-chlorophenyl isocyanate, compounds of this type are probable intermediates in the formation of the amines (271). It is worth noting however, that one instance is known in which phenyl isocyanate appears to react with an N-oxide in a different manner. 1,2-Dimethylbenzimidazole 3-N-oxide (276) in which the 2-position is blocked affords the N-phenylamino-derivative (277), presumably by a process involving nucleophilic substitution.¹⁴⁴



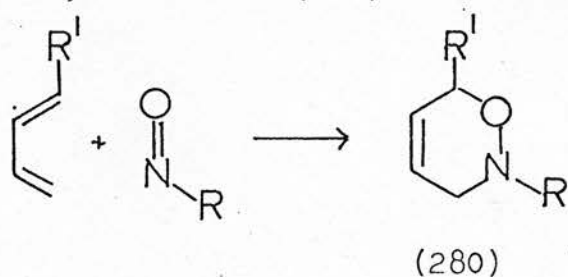
It can be seen from the present results that 1,3-dipolar cycloaddition is a useful route to 2-arylamino-quinoxalin-3(4H)-ones (271). Nucleophilic displacement of the 2-chloro-group in 2-chloro-4-methylquinoxalin-3(4H)-one (273) by arylamines appears to be the only alternative method. The reactivity of the 2-chloro-compound (273) towards nucleophilic displacement by amines was shown to be quite general. Heating with benzylamine and diethylamine afforded the corresponding amino-derivatives (274) and (275). The compound (275) was isolated as an oil and was characterised

as its picrate. Attempted displacement of the 2-chloro-group in compound (273) with ethyl carbamate was, however, unsuccessful.

Carbon disulphide has been widely used as a dipolarophile in 1,3-dipolar cycloaddition reactions but failed to react with the N-oxide (270b). None of the thiol (279), derived by loss of COS from the intermediate adduct (278) could be detected in the reaction mixture.

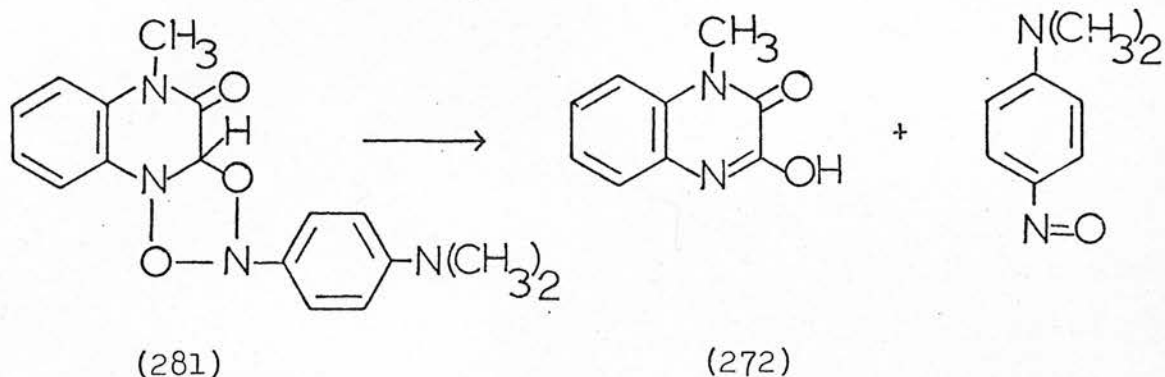


Kresze¹⁷³ has shown that 2 + 4 cycloaddition is a good method for the preparation of heterocyclic compounds when the dienophile contains heteroatoms. Aromatic nitroso compounds react readily with dienes in this way to afford 3,6-dihydro-1,2-oxazines (280).

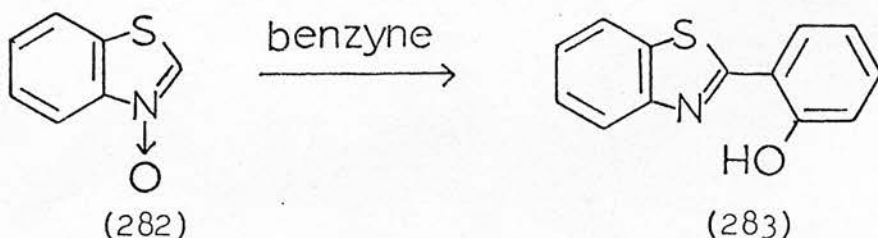


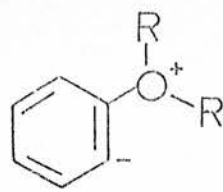
It was therefore of interest to see if this reactivity could be extended to 1,3-dipolar cycloadditions. Nitroso compounds do not appear to have been studied in this context.

p-Nitroso-N,N-dimethylaniline could in theory react with the N-oxide (270b) to yield the adduct (281). Alternatively, ring-opening of the adduct (281), as shown, might be expected to yield the 2-hydroxy-derivative (272) with re-generation of the nitroso compound. However, an attempt to condense the N-oxide (270b) with p-nitroso-N,N-dimethylaniline was unsuccessful.

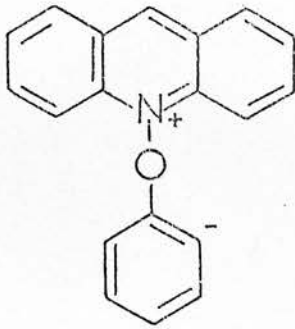


Many examples are known of 1,3-dipoles reacting with dipolarophiles containing a triple bond such as methyl propiolate. The inclusion of benzyne in these studies has opened up preparative routes to many benzo-heterocycles. Ethers and cyclic ethers are known to react with benzyne to form betaines of the type (284). The oxygen atom in heterocyclic N-oxides is even more basic and should therefore react with benzyne even more readily. Recently, Kano¹⁷⁴ has shown that benzothiazole 3-N-oxide (282) reacts with benzyne to form the hydroxyphenyl derivative (283).

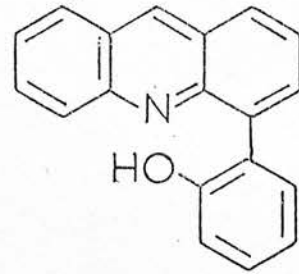




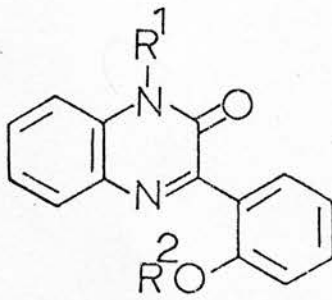
(284)



(285)

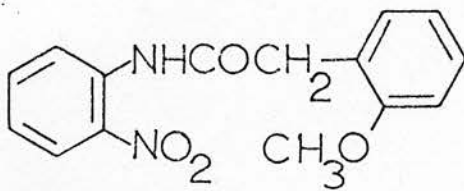


(286)

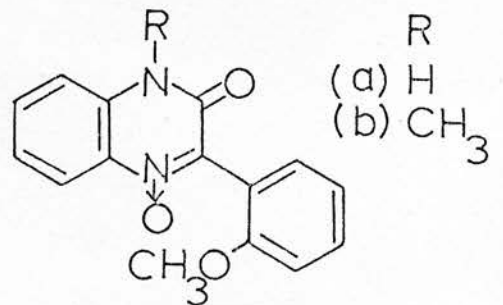


(287)

	R^1	R^2
(a)	H	H
(b)	CH ₃	H
(c)	H	CH ₃
(d)	CH ₃	CH ₃



(288)

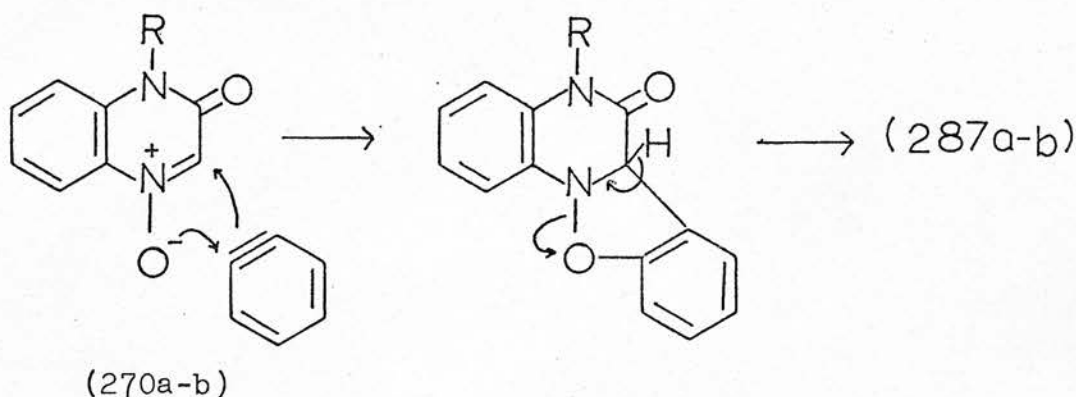


(289)

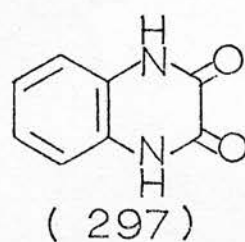
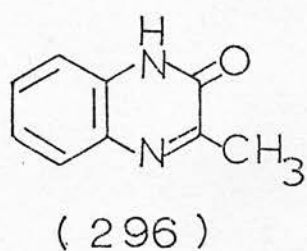
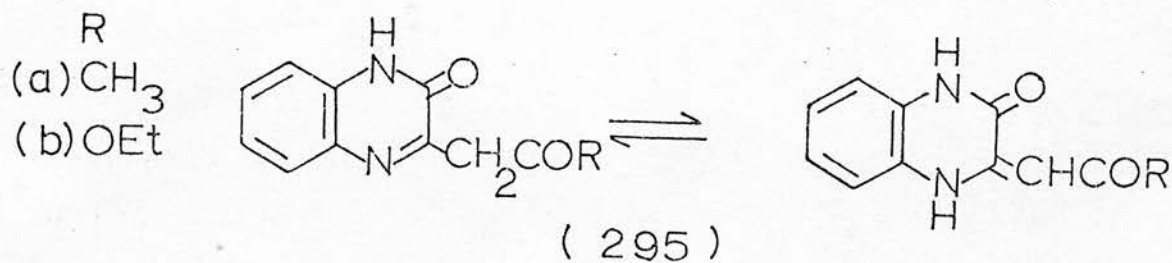
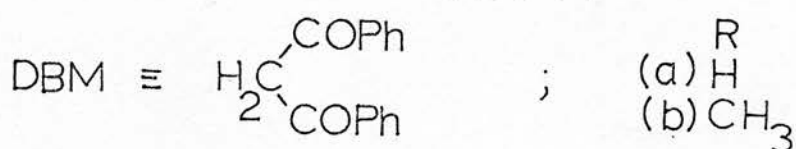
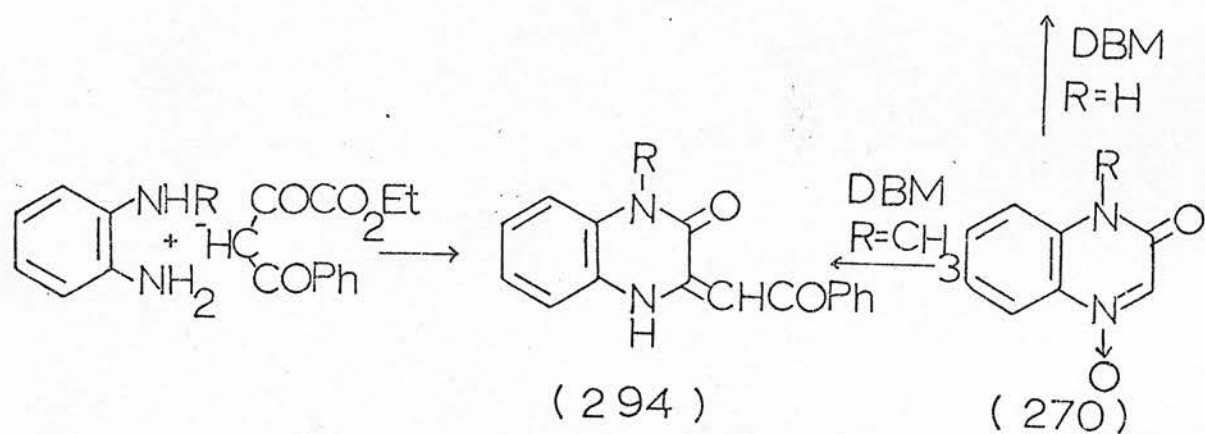
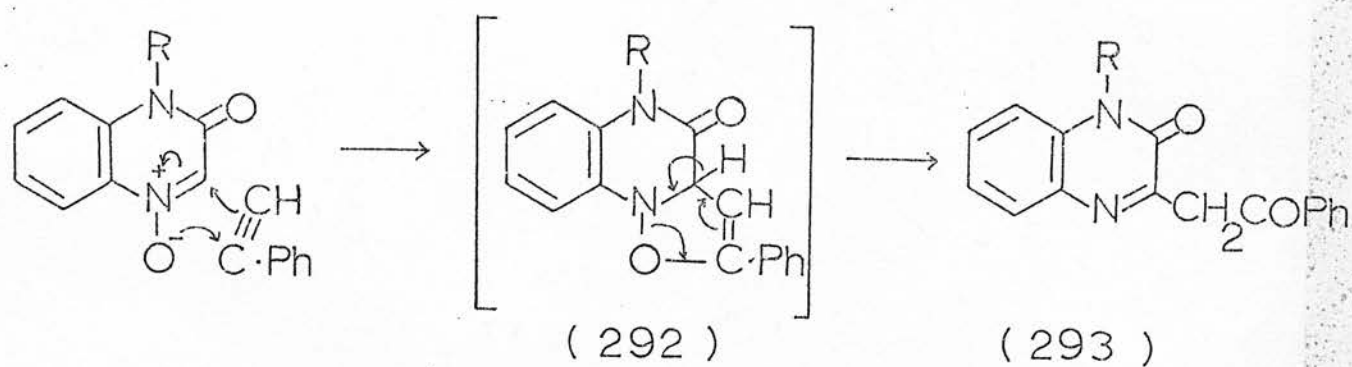
	R
(a)	H
(b)	CH ₃

Likewise, acridine 10-N-oxide reacts with benzyne to give the compound (286) in 25% yield.¹⁷⁵ The first step in this reaction may well be generation of the betaine (285) but subsequent steps are not yet clear.

When the N-oxides (270a-b) were heated in the presence of benzyne, generated by the aprotic method,¹⁷⁶ quantitative or near quantitative yields of products were obtained. These products were soluble in alkali and gave a deep red colour with iron (III) chloride in ethanol. This evidence suggested the presence of a phenolic group and hence the structures (287a-b) for the products.



The product derived from the N-oxide (270a) was methylated to afford a compound identical with that obtained from the N-oxide (270b) and benzyne. Further methylation afforded a dimethyl derivative. This dimethyl derivative is assigned the structure (287d) on the basis of its unambiguous synthesis. Condensation of 2-methoxyphenylacetyl chloride with o-nitroaniline yielded the anilide (288). Cyclisation¹⁴⁹ under basic conditions afforded the 1-N-oxide (289a) in poor yield. The major products of this reaction were o-nitroaniline and 2-methoxyphenylacetic acid, formed by hydrolysis of the anilide (288). Hydrolysis rather than cyclisation of the



anilide (288) is presumably due to deactivation of the methylene group in the side-chain by the o-methoxyphenyl substituent.

Dithionite reduction of the 1-N-oxide (289a) afforded the quinoxalin-3(4H)-one (287c) which was isomeric with the product derived from the N-oxide (270b) and benzyne, but had different properties. Methylation of the N-oxide (289a), followed by dithionite reduction afforded the compound (287d) which proved to be identical with the product of complete methylation of both compounds obtained by reaction of the N-oxides (270a-b) with benzyne.

It is well known that 1,3-dipolar cycloaddition reactions occur with alkenes and alkynes, particularly those substituted with electron-withdrawing groups (e.g. $C\equiv N$, CO_2R). The reactivity of aryl alkynes does not appear to have been studied in this respect. Phenylacetylene might be expected to react as a dipolarophile with the N-oxides (270a-b). Potentially, this reaction could afford two different products depending on the mode of addition of the acetylene derivative. The ketones (293) would arise from the adducts (292) whereas if addition occurs in the opposite direction to give the adducts (290), the aldehydes (291) would be the final products. The N-oxides (270a-b) were found to react readily with phenylacetylene (see later). However, unambiguous synthesis of the ketones (293) has shown them to be different from the products obtained from the N-oxides (270a-b) and phenylacetylene.

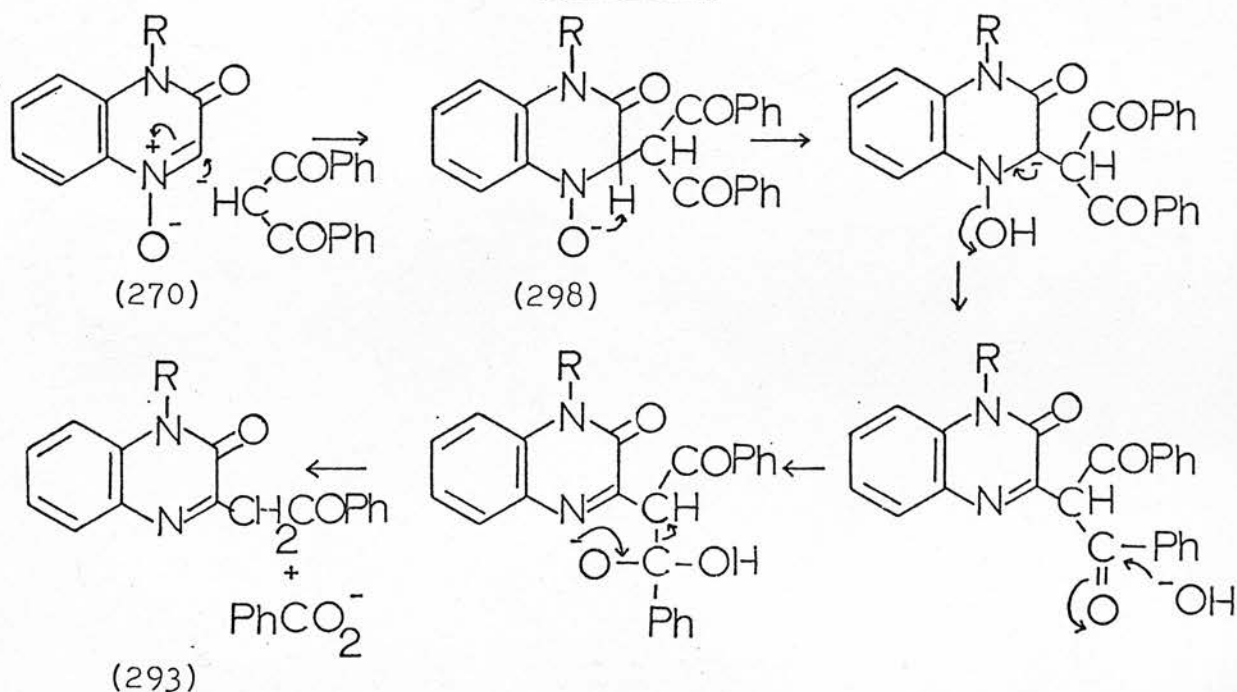
Condensation of o-phenylenediamine with ethyl benzoyl-

pyruvate afforded a yellow solid which analysed correctly for the ketone (293a). In support of this structure alkaline hydrolysis with 20% aqueous potassium hydroxide afforded 2-methylquinoxalin-3(4H)-one (296) and benzoic acid. Also, chromic acid oxidation yielded quinoxalin-2,3(1H,4H)-dione (297) and benzoic acid. However, the ^1H n.m.r. spectrum run in deuterated dimethylsulphoxide or in trifluoroacetic acid contained no absorption attributable to a methylene group. Other investigators^{177,178} have shown that quinoxalin-3(4H)-ones of the type (295) can exist in the two possible tautomeric forms shown, the predominant form depending on the solvent. Examination of the ^1H n.m.r. spectrum of the compound (295b) in deuterated dimethylsulphoxide indicated that in this solvent the predominant tautomer was that with the exocyclic double bond. On the other hand, in trifluoroacetic acid the alternative tautomer predominates. For the methyl ketone (295a) the predominant tautomer in both solvents is the form with the exocyclic double bond. Comparison of these spectra with that of the condensation product above showed that the yellow ketone existed solely in the tautomeric form (294a). Condensation of N-methyl-o-phenylenediamine with ethyl benzoylpyruvate afforded the corresponding N-methyl-derivative (294b) whose ^1H n.m.r. spectrum also possessed a signal attributable to an olefinic proton. The compound (294b) was also obtained by methylation of the quinoxalone (294a).

The quinoxalin-3(4H)-one 1-N-oxides (270a-b) are

known¹⁷⁹ to react with methylene compounds, substitution occurring at the 2-position. By analogy, dibenzoylmethane might be expected to react with the N-oxides (270a-b) forming initial adducts (298) convertible into the ketones (293) as shown (Scheme 11).

Scheme 11



The N-oxide (270a) condensed readily with dibenzoylmethane in the presence of piperidine to afford a yellow solid, identical with the yellow ketone (294a), but amounting to only 2% of the product. The main product was a white solid, isomeric with the yellow ketone (294a). In reactions similar to those of the latter, the white solid was converted by treatment with 20% aqueous potassium hydroxide and chromic acid into the quinoxalones (296) and (297) respectively. On the basis of these transformations and the presence of signals attributable to a methylene group in the ^1H n.m.r.

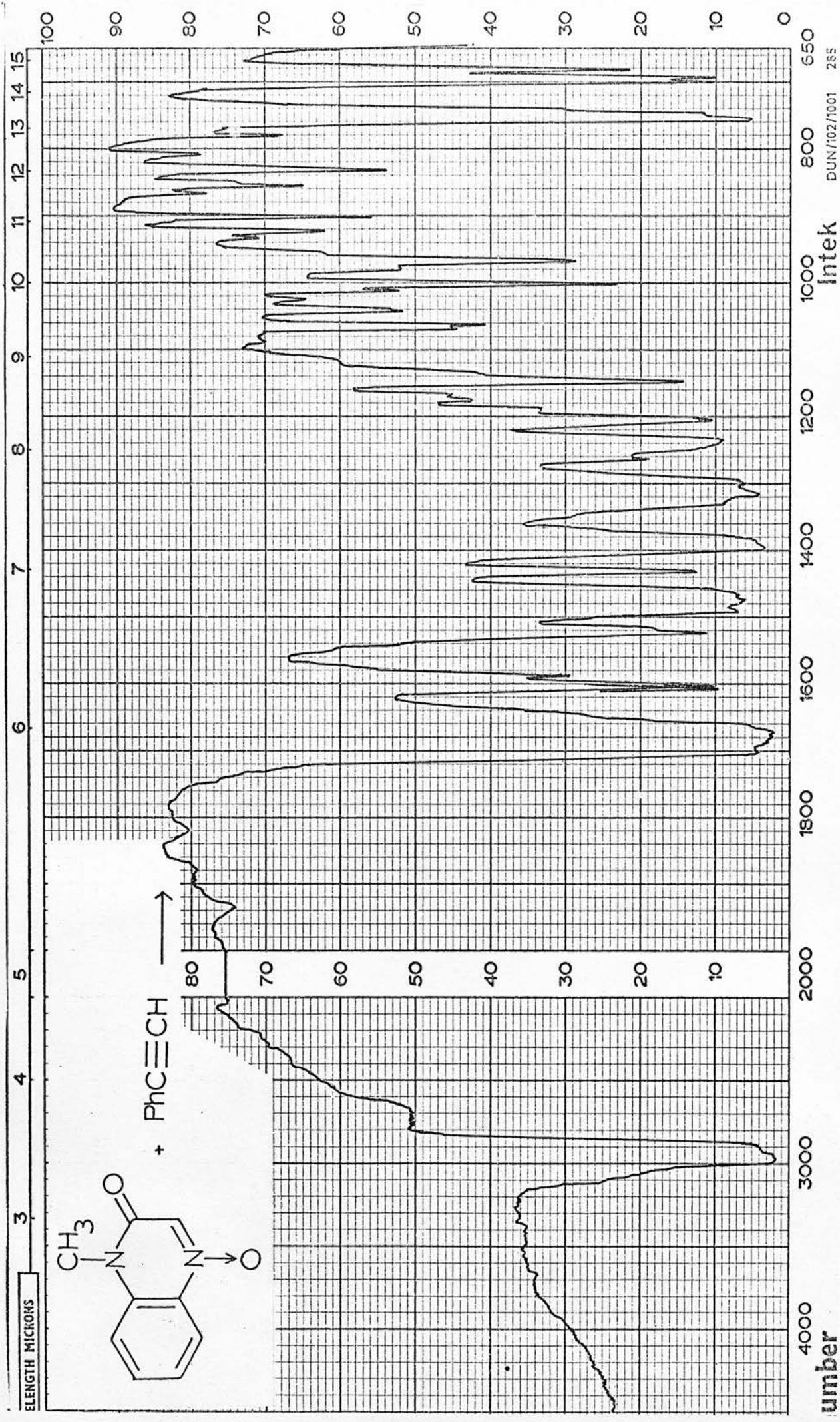


Figure 31.

spectrum, this white product is assigned the structure (293a). Thus it would appear that the tautomeric ketones (293a) and (294a) are capable of separate existence as discrete molecules. In an attempt to interconvert these tautomers the white ketone (293a) was warmed with 10% aqueous sodium hydroxide. However, it was recovered unchanged on acidification. Attempted methylation of the tautomer (293a) was unsuccessful and it may be significant that the reaction of the N-oxide (270b) with dibenzoylmethane afforded only the tautomeric form (294b). No trace was found of the alternative tautomer (293b).

The N-oxide (270a) when heated with phenylacetylene, in dry xylene, afforded two products, Y and Z, which were separable because of their differing solubilities. Neither solid was identical with either of the tautomeric ketones (293a) or (294a), nor did they show properties expected for the aldehyde (291a) which could result from addition of phenylacetylene across the nitron in the opposite direction. The mass spectrum of the more insoluble of the two products, (Y), indicated that its molecular weight was twice that expected for either of the ketones (293a) or (294a). However, the elemental analysis did not fit a dimeric structure. The ¹H n.m.r. spectrum of this compound contains two singlets in the olefinic region. The more soluble product, (Z), has the molecular formula, $C_{16}H_8N_2O_2$ and possesses only aromatic protons. Chromic acid oxidation of this compound afforded quinoxalin-2,3-(1H,4H)-dione (297), showing that it still retains the quinoxaline nucleus.

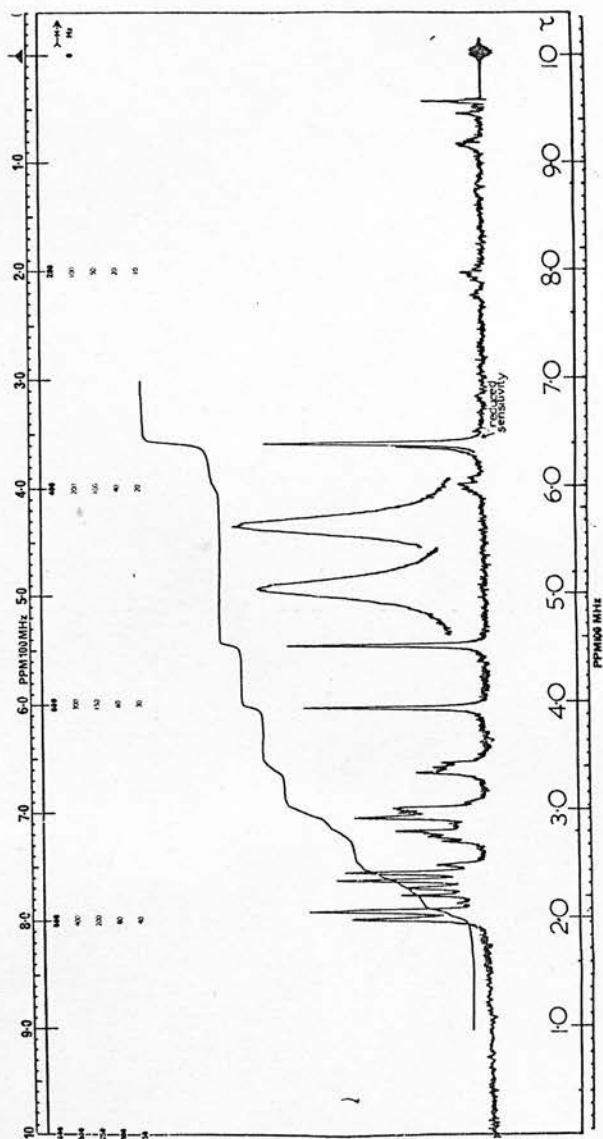


Figure 32. ^1H n.m.r. spectrum of compound X in trifluoroacetic acid at 100 MHz; inset expansion to 250 kHz.

The N-oxide (270b) reacted with phenylacetylene to give only one solid product, X, which was not identical with the ketone (294b). Its i.r. spectrum (Figure 31) showed that possibly several carbonyl groups were present and its ^1H n.m.r. spectrum (Figure 32) contains two singlets in the olefinic region. The molecular weight (556) of this product again indicates a dimeric structure and shows that each of the singlets in the ^1H n.m.r. spectrum are equivalent to two protons. Thus the product could be a symmetrical dimer and these peaks could each correspond to a single uncoupled olefinic proton. Alternatively, if the product is unsymmetrical, these signals could indicate the presence of two different methylene groups in the molecule.

In order to solve the structural problem posed by the products X and Y, degradation was attempted. However, compound X was stable to reduction with sodium dithionite, iron filings in acetic acid or catalytic hydrogenation, showing that the oxygen present in the molecule is not there in the form of an N-oxide group. The compound, X, was also stable to heating with 20% (w/v) aqueous sulphuric acid, and was recovered essentially unchanged on heating with 10% aqueous sodium hydroxide. Heating with potassium hydroxide in trigol resulted in decomposition to a dark oil, shown by T.L.C. to contain at least six components. Chromic acid oxidation of X afforded a product which was not a recognisable molecule and whose elemental analysis could not be fitted to a molecular formula.

This is the stage at which this problem now stands. Having met with little success, the broad degradative approach initially attempted, will have to be modified. Until such time as further work can be done in this direction no positive structural assignments can be made for the products obtained from the N-oxides (270a-b) and phenylacetylene.

SECTION FOUR

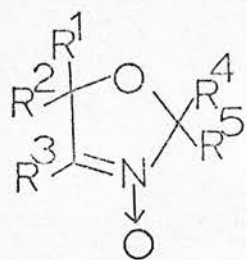
SOME STUDIES ON THE SYNTHESIS AND 1,3-DIPOLAR
CYCLOADDITION REACTIONS OF OXAZOLE 3-N-OXIDES

SOME STUDIES ON THE SYNTHESIS AND 1,3-DIPOLAR CYCLO-
ADDITION REACTIONS OF OXAZOLE 3-N-OXIDES

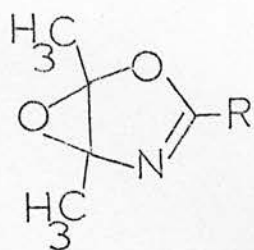
STUDIES OF THE DIELS-DILTHEY SYNTHESIS OF OXAZOLE 3-N-OXIDES

Many synthetic routes are available for the preparation of oxazoles but oxazole 3-N-oxides are more difficult to obtain and hence have been little studied. Unlike many other ring systems, oxazoles do not readily form N-oxides on treatment with peracids. An example has recently been recorded¹⁸⁰ of the formation of 3-oxazoline N-oxides (298) by treatment of the corresponding base with m-chloroperbenzoic acid. However, oxazole 3-N-oxides have apparently not been prepared in this way. Some oxazole 3-N-oxides are relatively unstable and would presumably break down on attempted synthesis from the oxazole by peracid oxidation. The only known synthetic route to oxazole 3-N-oxides involves the condensation of α -oximino ketones with aldehydes in the presence of hydrogen chloride. This method was first employed by Diels and Riley¹⁸¹ and subsequently extended by Dilthey and Friedrichsen.¹⁸² However, these authors formulated the products of the condensation of biacetyl monoxime with aryl aldehydes as the epoxides (299) rather than N-oxides. Cornforth and Cornforth¹⁸³ later suggested that these compounds had the oxazole 3-N-oxide structure (301). The correctness of the N-oxide formulation¹⁸³ has since been established by i.r. and u.v. spectral evidence and chemical behaviour.¹⁸⁴

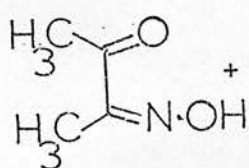
The oxazole 3-N-oxide (301a) had been shown to react with phenyl isocyanate but the structure of the product was



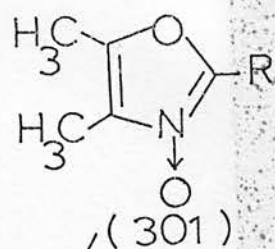
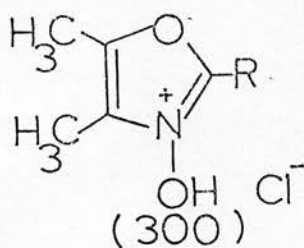
(298)



(299)

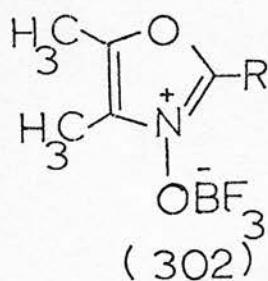


+ R·CHO



R

- (a) Ph
- (b) p-Cl·C₆H₄
- (c) p-OCH₃·C₆H₄
- (d) p-CH₃·C₆H₄
- (e) o-OH·C₆H₄
- (f) m-NO₂·C₆H₄
- (g) p-NO₂·C₆H₄
- (h) p-N(CH₃)₂·C₆H₄
- (j) CH₃



in dispute.^{181,183} Because of our interest in 1,3-dipolar cycloaddition reactions (see Section 3) it was decided to reinvestigate the reactivity of oxazole 3-N-oxides towards dipolarophiles such as phenyl isocyanate and if possible to establish unequivocally the structure of the products.

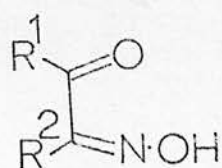
Although the synthesis of oxazole 3-N-oxides, described above, was well documented, its use appeared to be restricted to the preparation of 2-aryl-4,5-dialkyloxazole 3-N-oxides such as (301). Recently, however, it has been reported¹⁸⁵ that condensation of α -oximino ketones such as (303j) with benzaldehyde affords 4-acetyloxazole 3-N-oxide hydrochlorides. However the free N-oxides were not obtained in these instances. It was thus of interest to investigate the application of the Diels-Dilthey oxazole N-oxide synthesis to aliphatic aldehydes and other oximino derivatives.

Biacetyl monoxime condensed readily with substituted benzaldehydes in the presence of hydrogen chloride to give the oxazole 3-N-oxides (301). The N-oxides (301a-e) were isolated as their hydrochlorides (300a-e) by diluting the reaction mixture with ether. Treatment of these hydrochlorides with dilute ammonium hydroxide readily afforded the free N-oxides (301a-e). It was found that these N-oxides formed hydrates, convertible to the free N-oxides by storage over phosphorus pentoxide. As previously reported¹⁸² the oxazole 3-N-oxides (301a), (301c) and (301e) were sensitive to light and air, tending to discolour and decompose to gums. The previously unreported N-oxides (301b) and (301d) behaved similarly. Satisfactory analytical data could not be obtained

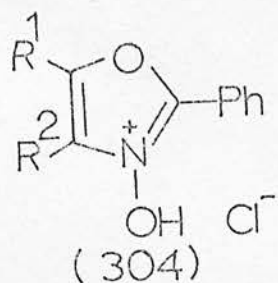
for the p-tolyl derivative (30ld) presumably due to its instability in air. The i.r. spectra and ^1H n.m.r. spectra (Table 7) of the N-oxides (30lb) and (30ld) were in accord with the assigned structures.

The m-nitro- and p-nitrophenyl derivatives (30lf-g) were obtained directly from the reaction mixture by dilution with water,¹⁸² no hydrochlorides being formed in these cases. The reaction mixture from the condensation of p-N,N-dimethylaminobenzaldehyde and biacetyl monoxime had to be evaporated and treated with ether to afford the hydrochloride (300h). Careful trituration and stirring with dilute ammonium hydroxide was employed to generate the free N-oxide (30lh) from the hydrochloride (300h). Trace amounts of unreacted aldehyde were detected in the ^1H n.m.r. spectrum of the crude product and were removed by crystallisation.

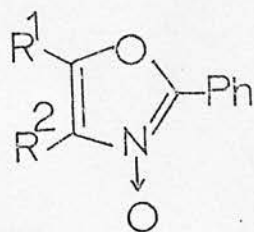
In an attempt to extend this synthetic method to aldehydes other than aromatic aldehydes, biacetyl monoxime was reacted with acetaldehyde in the presence of hydrogen chloride. The i.r. spectrum of the solid product indicated that it was a hydrochloride and the ^1H n.m.r. spectrum (Table 7) contained signals at τ 7.14, 7.57 and 7.68 due to three non-equivalent methyl groups. The product was unstable to crystallisation but on the basis of its spectral properties it is formulated as 2,4,5-trimethyloxazole 3-N-oxide hydrochloride (300j). Attempts to convert the hydrochloride (300j) by treatment with a variety of bases (dilute ammonia, sodium bicarbonate, sodium acetate) into the N-oxide (30lj) were either unsuccessful or afforded gums containing several



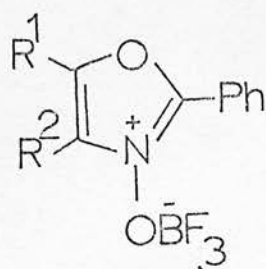
(303)



(304)

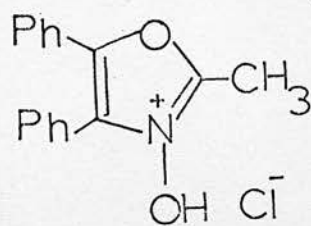


(305)

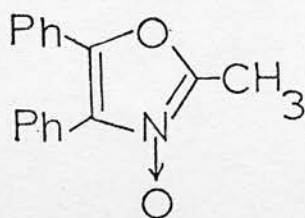


(306)

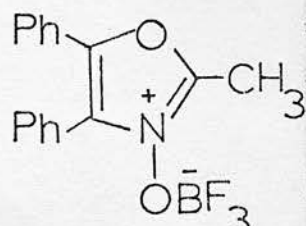
	R^1	R^2
(a)	Ph	CH_3
(b)	CH_3	Ph
(c)	Ph	H
(d)	CH_3	H
(e)	Ph	CN
(f)	CH_3	CO_2Et
(g)	CH_3	CO_2H
(h)	Ph	CO_2Et
(j)	CH_3	COCH_3
(k)	C_2H_5	CH_3



(307)



(308)



(309)

components. Attempts to form stable adducts of the N-oxide (301j) by treating the hydrochloride (300j) with picric acid or boron trifluoride etherate were also unsuccessful. Thus it would appear that, although the condensation of biacetyl monoxime with aromatic aldehydes is a general reaction, the presence of at least one aromatic ring is essential to the stability of the N-oxide product.

The effect of varying the oxime component while keeping the aldehyde component constant was next studied by condensing a series of oximino compounds (303) with benzaldehyde in the presence of hydrogen chloride.

The oximino compound (303a) readily formed the 4-methyl-5-phenyloxazole 3-N-oxide (305a)¹⁸² but as reported by Dilthey and Friedrichsen¹⁸² the isomeric oximino compound (303b) afforded a dark, intractable oil rather than the corresponding N-oxide (305b) which is presumably unstable in the reaction medium.

The application of the Diels-Dilthey synthesis to the preparation of oxazole 3-N-oxides unsubstituted in the 4-position was largely unsuccessful. Condensation of 2-oximinoacetophenone (303c) with benzaldehyde in the presence of hydrogen chloride afforded a solid product but in insufficient amount for characterisation. The ¹H n.m.r. spectrum was unrevealing due to the signal overlap in the aromatic region. However the product is assigned the N-oxide structure (305c) since its i.r. spectrum was identical with the compound obtained by treating the boron trifluoride adduct (306c) with sodium dithionite (see later). The oximino

compound (303d) reacted with benzaldehyde to afford a hygroscopic, pale yellow solid. The hydrochloride structure (304d) for this product is supported by its i.r. and ^1H n.m.r. spectra. However, attempts to liberate the free N-oxide (305d) from the hydrochloride (304d) or to convert it into a stable boron trifluoride adduct were unsuccessful.

An attempt was next made to adapt the Diels-Dilthey synthesis for the preparation of oxazole 3-N-oxides possessing a functional group at C(4). Attempted condensation of the oximino cyano-compound (303e) with benzaldehyde was, however, unsuccessful and resulted in recovery of the starting material. The oximino ester (6f) reacted readily with benzaldehyde in the presence of hydrogen chloride to afford a hygroscopic hydrochloride (304f) which could not be converted into the N-oxide (305f) by treatment with dilute ammonium hydroxide. However, treatment with sodium acetate afforded the N-oxide (305f) as a white solid. The i.r. and ^1H n.m.r. spectra (Table 1) of the compounds (304f) and (305f) were in accord with the assigned structures. However, the N-oxide (305f) was very unstable and rapidly decomposed to a yellow gum on standing for a short time at room temperature. The ^1H n.m.r. spectrum of this gum indicated that several components were present and that the N-oxide (305f) decomposed too rapidly to be studied further. Immediate analysis of this N-oxide gave analytical data in accord with the structure (305f). Also, immediate treatment of a solution of the N-oxide (305f) in acetic acid with boron trifluoride etherate afforded a stable boron trifluoride adduct (306f).

Hydrolysis of the hydrochloride (304f) by warming briefly with 10% aqueous sodium hydroxide afforded the corresponding carboxylic acid (305g) which, unlike the ester (305f), was a stable molecule. In contrast to (303f), the oximino compound (303h) failed to react with benzaldehyde in the presence of hydrogen chloride. The poor yield of oxazole N-oxide obtained from (303c) and the failure of the oximino compounds (303e) and (303h) to react at all, demonstrates the lower reactivity of a benzoyl group relative to an acetyl group.

Although the N-oxide (301j) from biacetyl monoxime and acetaldehyde could only be isolated as the crude hydrochloride (300j), it was thought that the stabilising effect of the two phenyl groups in benzil monoxime would permit extension of the hydrogen chloride method to include acetaldehyde and hence the synthesis of the 2-methyl-N-oxide (308). However, this N-oxide was only obtained in a crude form as its hydrate. Attempted crystallisation caused decomposition and after drying in vacuo over phosphorus pentoxide, exposure to air caused immediate decomposition to a gum which yielded benzil on trituration with cold, aqueous sodium hydroxide.

From these results it can be seen that whilst some success was achieved in extending the Diels-Dilthey synthesis, the low yields obtained and the difficulties encountered in the isolation of the free N-oxides (305) show that this synthetic route to oxazole 3-N-oxides is relatively inflexible.

In the light of the observation that the N-oxide (305f) formed a stable boron trifluoride adduct (306f) it was decided

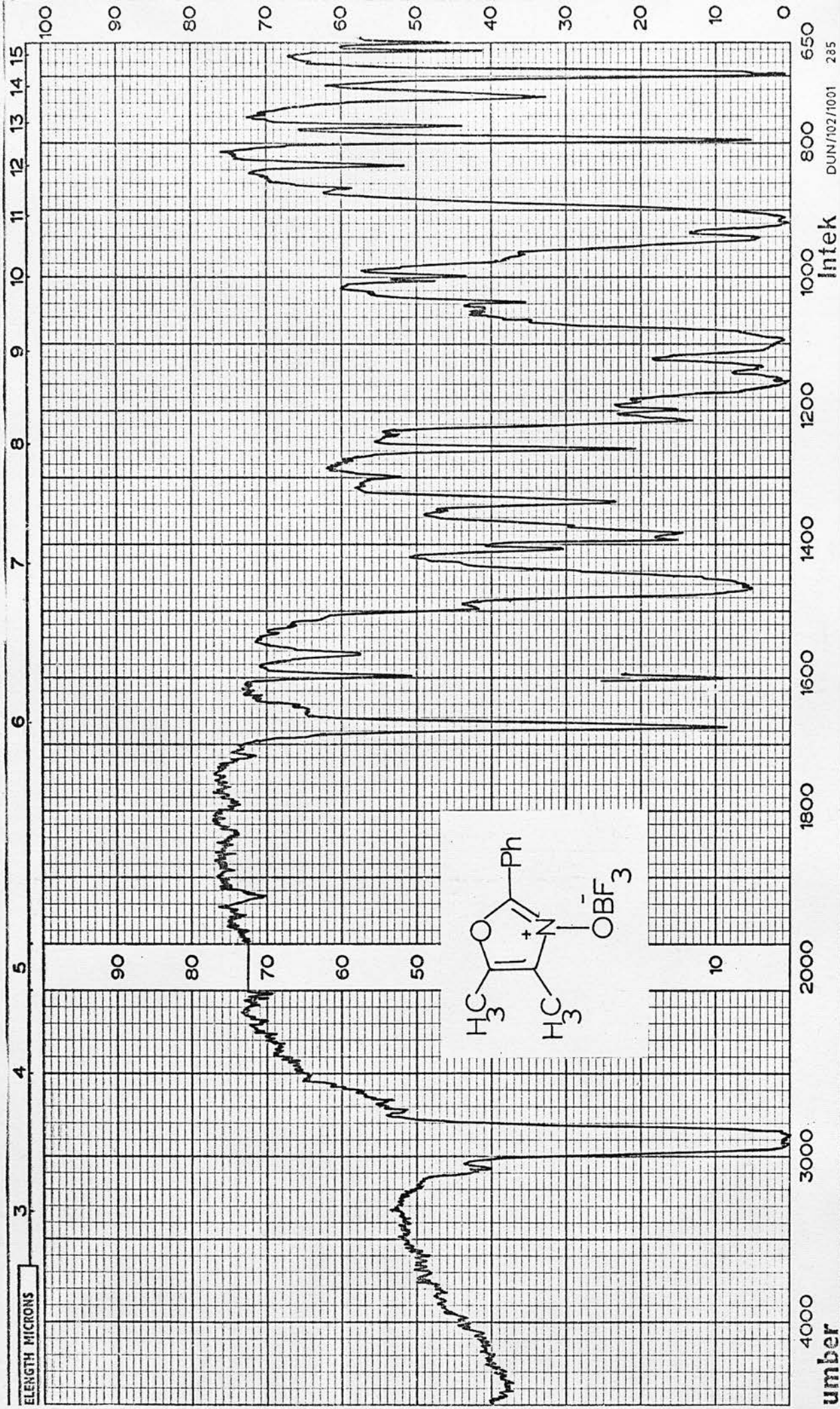


Figure 33 .

to examine the formation of this type of adduct from oxazole 3-N-oxides. Many types of heterocyclic N-oxide form boron trifluoride adducts.^{15,16} The stability of these adducts can vary somewhat but generally they are readily reconverted into the corresponding N-oxides. This was shown to be the case for the quinoxalin-3(4H)-one 1-N-oxide boron trifluoride adduct (249) which reverted to the N-oxide (216a) on attempted crystallisation. The N-oxide (301a), when treated with boron trifluoride etherate afforded a white crystalline solid whose mass spectrum showed a parent ion corresponding to the N-oxide (301a) though small peaks at m/e 10 and m/e 11 showed the presence of boron. Also, the i.r. spectrum (Figure 33) was not identical with that of the N-oxide (301a) and the ^1H n.m.r. spectrum (Table 1) and elemental analysis were in accord with its formulation as the adduct (302a). The adduct (302a) was stable to crystallisation from acetic acid but on heating with ethanol afforded a solid shown by its ^1H n.m.r. spectrum to be a complex mixture. The N-oxide (305a) likewise afforded a boron trifluoride adduct (306a) in quantitative yield. As previously mentioned, no adducts could be formed by treating the hydrochlorides (300j) and (304d) with boron trifluoride etherate.

The formation of stable boron trifluoride adducts from oxazole 3-N-oxides prompted a study of the condensation of oximino compounds with aldehydes using boron trifluoride as catalyst. Biacetyl monoxime and the oximino compounds (303a) and (303f) condensed readily with benzaldehyde in the presence of boron trifluoride to afford the corresponding

oxazole 3-N-oxide boron trifluoride adducts (302a), (306a) and (306f) in good yield. These adducts were identical with the products obtained by treating the corresponding N-oxides directly with boron trifluoride. The oximino compounds (303e) and (303h) which failed to react in the presence of hydrogen chloride, condensed with benzaldehyde in the presence of boron trifluoride to form the adducts (306e) and (306h). However, the yields of these adducts were low. The oximino compound (303b) which afforded an intractable oil by the hydrogen chloride method, condensed with benzaldehyde in the presence of boron trifluoride to yield the adduct (306b). The reaction time had to be kept relatively short, in this case, as decomposition occurred in the reaction medium. The use of boron trifluoride as catalyst did little to enhance the yield of the condensation of (303c) with benzaldehyde, the adduct (306c) being formed only in moderate yield. Although the oxazole 3-N-oxide hydrochlorides (300j) and (304d) could not be converted into the corresponding boron trifluoride adducts (302j) and (306d), the latter compounds were obtained by condensation of the corresponding oximino and aldehyde components in the presence of boron trifluoride. Similarly, benzil monoxime and acetaldehyde condensed in the presence of boron trifluoride to yield the adduct (309) which could not be formed directly from the N-oxide (308). The attempted condensation of the oximino compound (303j) with benzaldehyde in the presence of boron trifluoride afforded an intractable oil and was the only instance of the reactions attempted which failed to give a solid product by this method.

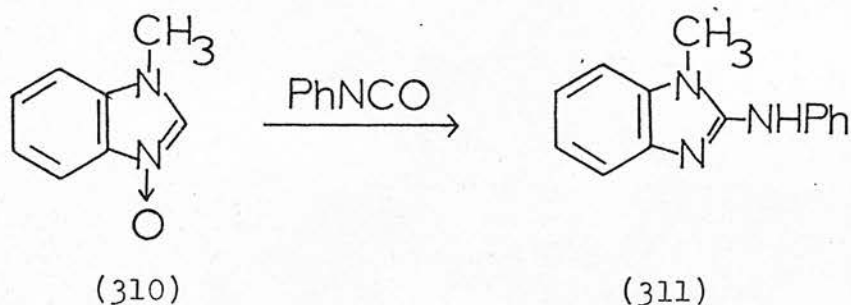
explain the rather surprising stability of the N-oxide group to dithionite reduction. Treatment of the boron trifluoride adduct (306a) with sodium dithionite similarly afforded the corresponding N-oxide (305a) but only a dark oil was obtained when this method was applied to the adduct (306b). Thus none of the methods studied is suitable for the synthesis of the N-oxide (305b). The 4-unsubstituted adduct (306c) reacted with sodium dithionite to afford a solid which was identical with that obtained by the hydrogen chloride method. This product decomposed on attempted crystallisation from benzene, but is assigned the N-oxide structure (305c) on the basis of its spectral properties. The small amount of solid obtained from the dithionite reduction of the adduct (306e) was insufficient for characterisation but did not appear to be the cyano-N-oxide (305e) since the i.r. spectrum contained absorption due to an amino-group.

In view of these latter results it is apparent that the boron trifluoride method offers no great advantage over the use of hydrogen chloride in the preparation of oxazole 3-N-oxides. It does appear, however, that oximino compounds and aldehydes condense more readily in the presence of boron trifluoride.

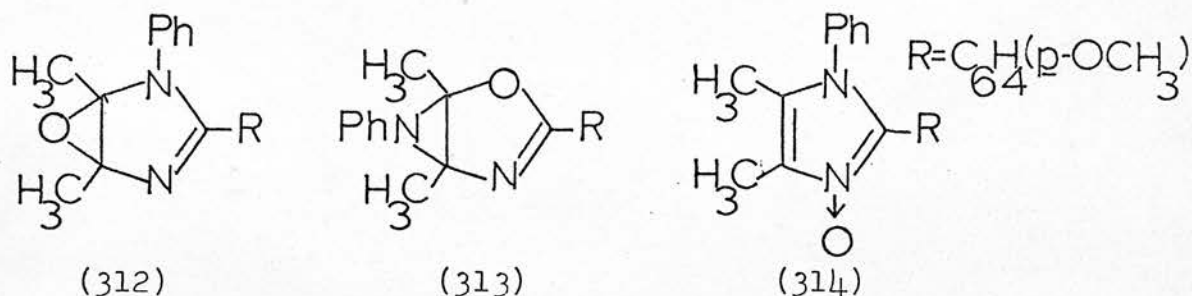
THE REACTIONS OF OXAZOLE 3-N-OXIDES WITH PHENYL ISOCYANATE

As described in the preceding Section, N-oxides having an adjacent unsubstituted position undergo 1,3-dipolar cycloaddition with phenyl isocyanate to afford 2-N-phenylamino derivatives such as (271). Relatively few examples of this

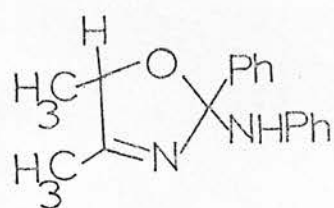
type of reaction are known in the case of azole N-oxides. Takahashi and Kano¹⁰² report the formation of 2-N-phenylamino-1-methylbenzimidazole (311) from 1-methylbenzimidazole 3-N-oxide (310) and phenyl isocyanate. In contrast, the corresponding reaction with 1,2-dimethylbenzimidazole 3-N-oxide (276) which is blocked at the 2-position is reported¹⁴⁴ to give the 6-N-phenylamino-derivative (277) (see Section 3, page 103).



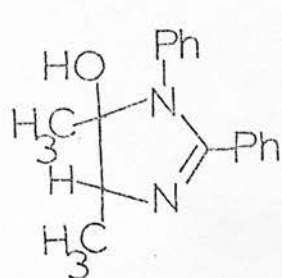
Diels and Riley¹⁸¹ were the first to examine the reaction of the 'oxidoöxazole' (299c) [which is now known to be the N-oxide (301c)] with phenyl isocyanate. They formulated the product obtained as either (312) or (313). This reaction was later examined by Cornforth and Cornforth¹⁸³ who assigned the structure (314) to the product.



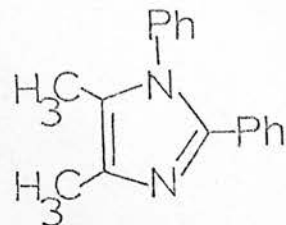
Since none of the structures was supported by firm experimental evidence, it was decided to investigate the reactions of oxazole 3-N-oxides with isocyanates with a view to determining



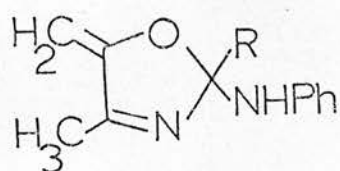
(319)



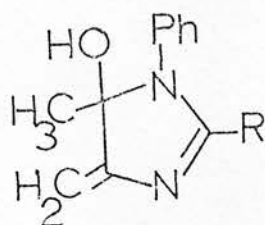
(320)



(321)



(315)



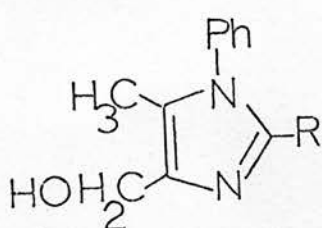
(316)

R
(a) Ph

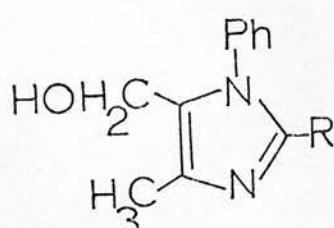
(b) p-Cl·C₆H₄

(c) p-OCH₃·C₆H₄

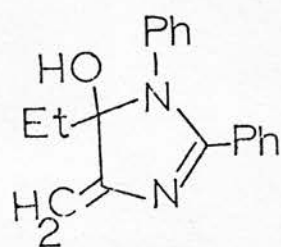
(d) p-CH₃·C₆H₄



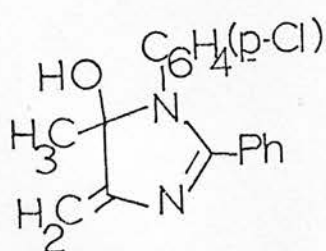
(322)



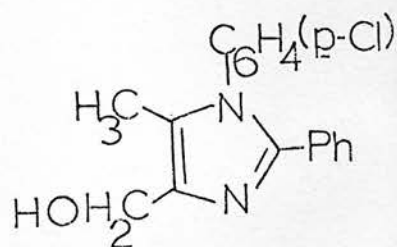
(323)



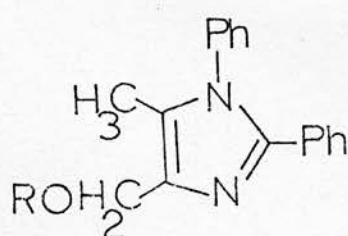
(324)



(325)



(326)



(327)

R
(a) Ac
(b) CH₃
(c) Et

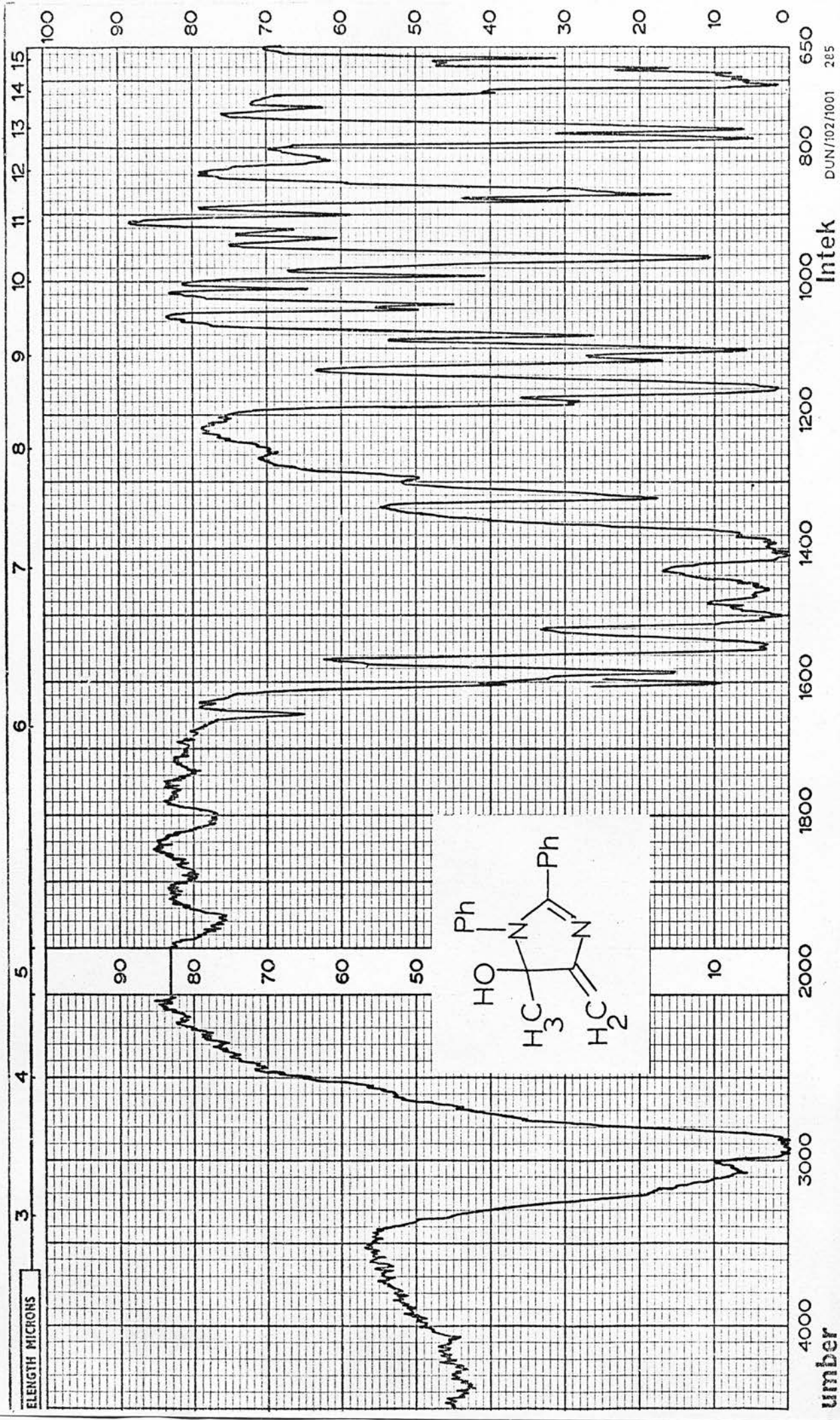
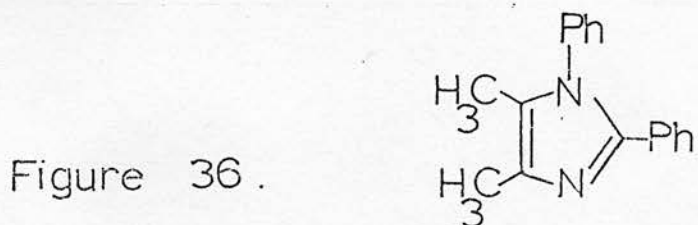
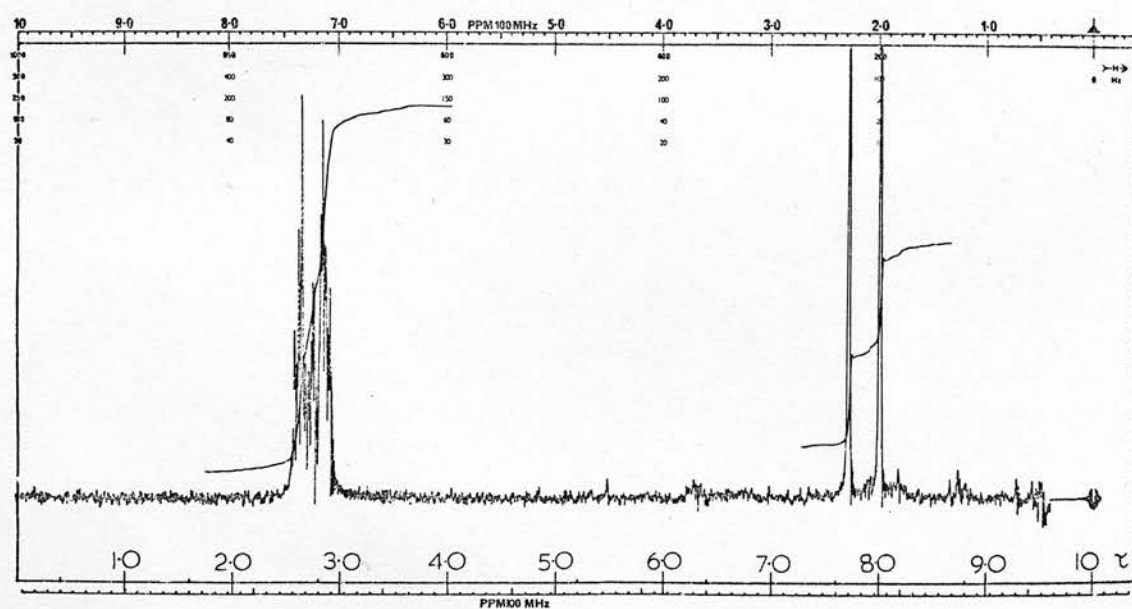
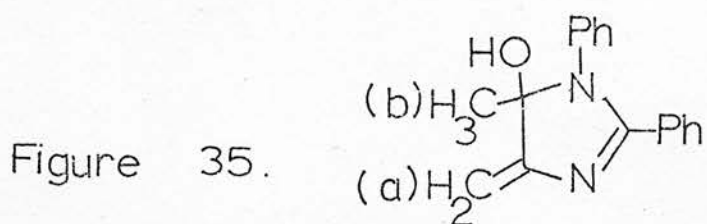
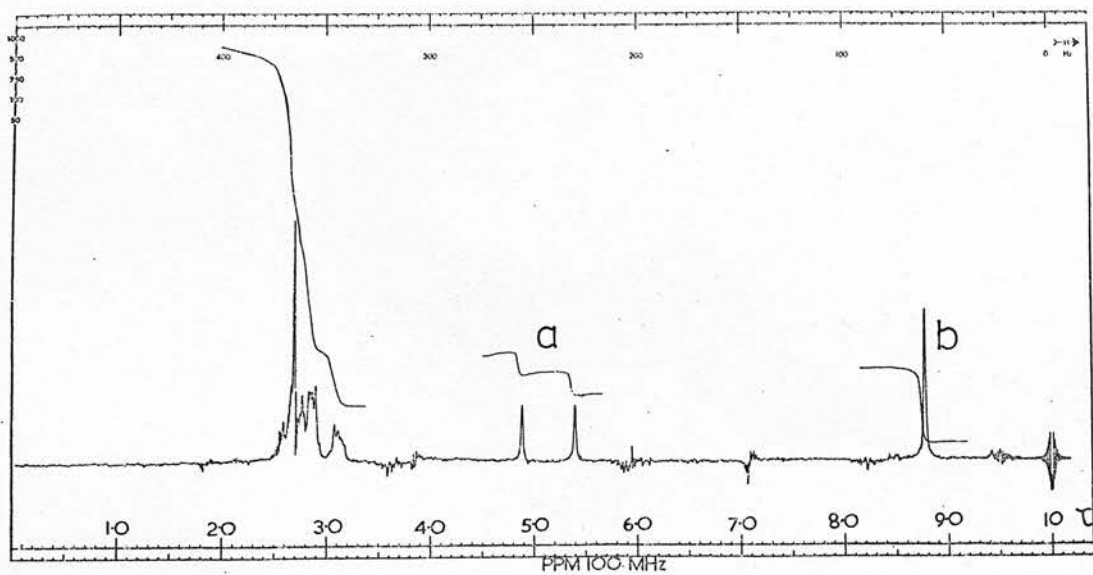


Figure 34



^1H n.m.r. spectra of compounds (316a) (Figure 35) and (321) (Figure 36) at 100 MHz in deuteriochloroform.

the structures of the products.

Reaction of 4,5-dimethyl-2-phenyloxazole 3-N-oxide (301a) with phenyl isocyanate occurred readily at room temperature with evolution of heat and gas. The white crystalline solid isolated from this reaction gave analytical data consistent with the molecular formula $C_{17}H_{16}N_2O$. This formula implies addition of phenyl isocyanate to the 3-N-oxide (301a) and subsequent loss of carbon dioxide. Examination of the 1H n.m.r. spectrum of the product (Table 8 and Figure 35) showed the presence of only one methyl signal thus excluding the previously assigned structures (312), (313) or (314). The spectrum also contains two singlets at τ 4.89 and 5.40 each integrating for one proton. This type of absorption is characteristic of a terminal methylene group.¹⁸⁶ Thus, at this stage it can be presumed that either the 4- or 5-methyl group of the starting oxazole 3-N-oxide (301a) has been transformed into a terminal methylene group. The i.r. spectrum of the product (Figure 34) possessed no carbonyl group and thus the oxygen atom in the product must be in a closed ring structure or in a hydroxyl group. On the evidence thus far two possible structures can be written for the product. 1,3-dipolar cycloaddition of phenyl isocyanate followed by abstraction of a hydrogen atom from the 5-methyl group and liberation of carbon dioxide as shown in Scheme 12 would give rise to the Δ^4 -oxazoline (315). Structures of a similar type are known.¹⁸⁰ However a structure of the type (315a) would be expected to be relatively unstable due to the presence of the imino-ether group.

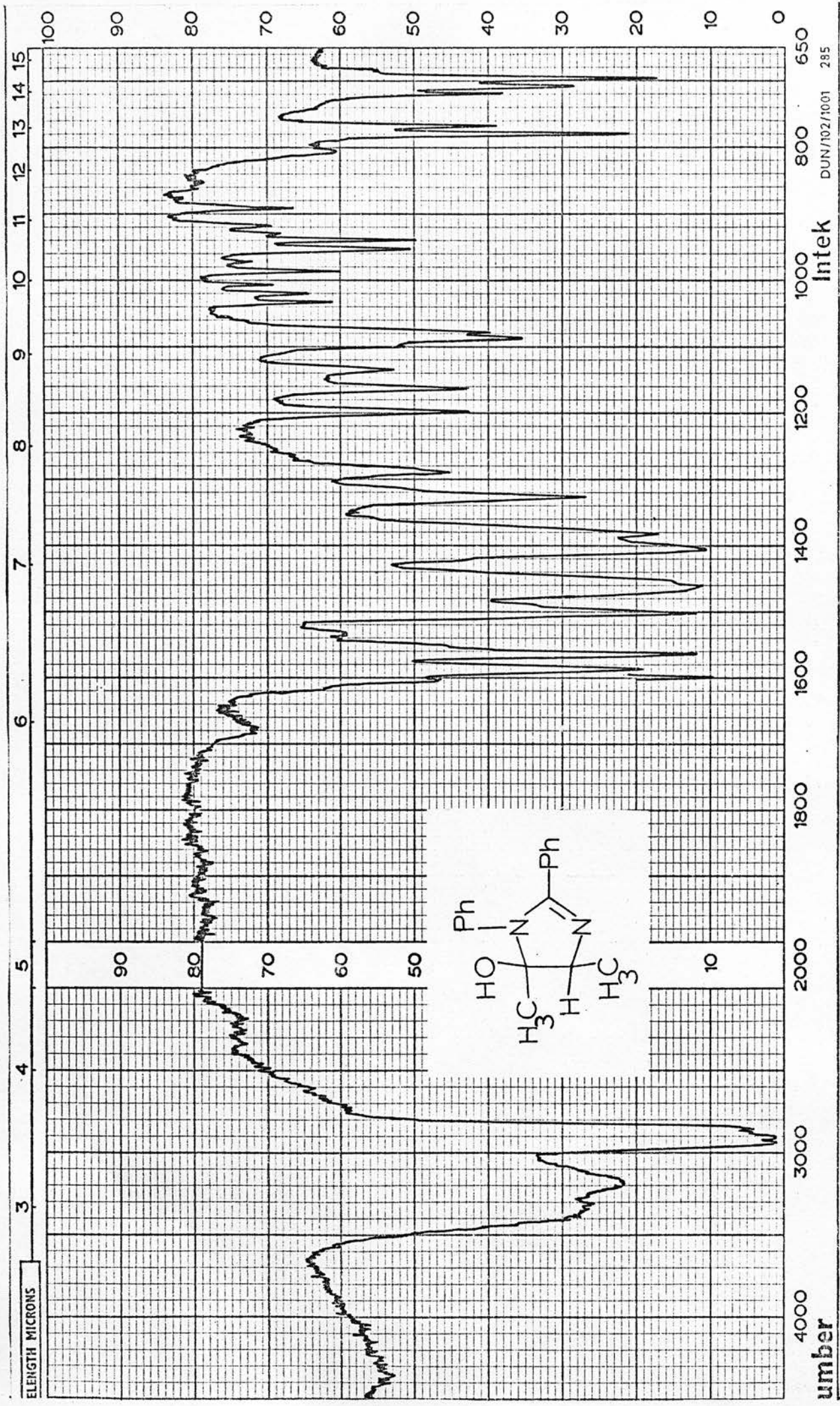
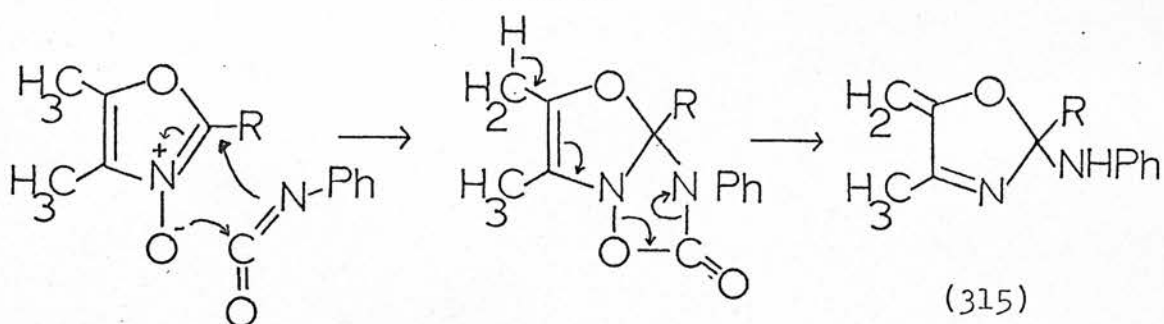


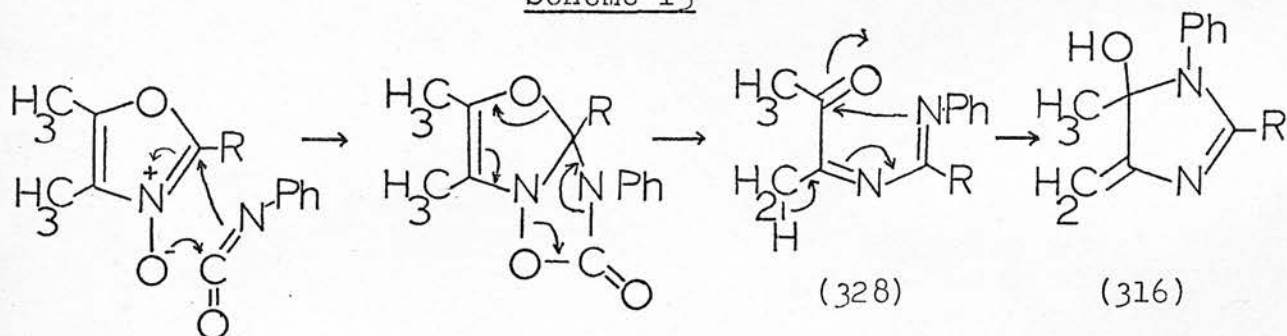
Figure 37.

Scheme 12

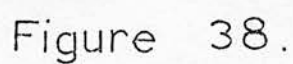
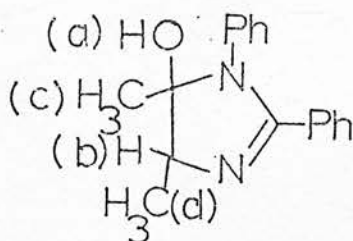


Alternatively, opening of the oxazole ring followed by re-cyclisation, as shown in Scheme 13 could give rise to the imidazole derivative (316a). Both structures (315a) and (316a) fit the spectral properties observed for the product and thus no distinction can be made between them without further evidence.

Scheme 13

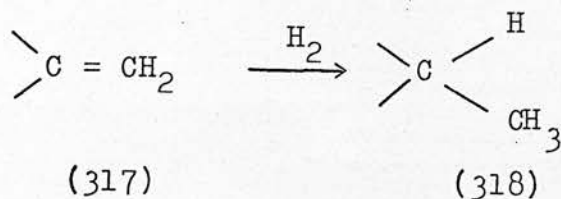


The presence of the terminal methylene group was further established by catalytic hydrogenation. One equivalent of hydrogen was taken up and the i.r. spectrum of the product (Figure 37) still contained no carbonyl group suggesting that any ring in the molecule had remained intact. The signals due to the terminal methylene group in the ^1H n.m.r. spectrum (Figure 38) of the adduct (315a) or (316a) were replaced in the hydrogenated compound by a quartet centred at τ 5.93 integrating for one proton and a doublet centred



¹H n.m.r. spectrum, plus spin-decoupling, of compound (320) at 100 MHz in deuteriochloroform.

at τ 8.71 integrating for three protons (see Figure 38). This suggested that the transformation (317) \rightarrow (318) had occurred.



Spin-decoupling confirmed that this was the case (see Figure 38). Irradiation at τ 5.93 resulted in the collapse of the doublet at τ 8.71 to a singlet, and irradiation at τ 8.71 caused the collapse of the quartet at τ 5.93 to a singlet. On the basis of this evidence either of the structures (319) or (320) can be assigned to the hydrogenation product. However, the presence of a singlet at τ 5.67 was thought more likely to be due to a hydroxyl group than a secondary amine thus favouring structure (320). Another point in favour of the structure (320) was that on standing in contact with ether, the hydrogenated compound (319) or (320) underwent dehydration. The product thus obtained analysed correctly for $\text{C}_{17}\text{H}_{16}\text{N}_2$, and the ^1H n.m.r. spectrum (Figure 36) contained signals (τ 7.73, 8.02) due to two methyl groups. It was thought likely, and later confirmed that the dehydration product was the imidazole derivative (321). Since it is unlikely that the oxazoline derivative (319) would rearrange and dehydrate simply on standing in contact with ether these results support the structures (320) and (316a) for the hydrogenation product and the phenyl isocyanate adduct. The attempted preparation of the imidazole derivative (321) by

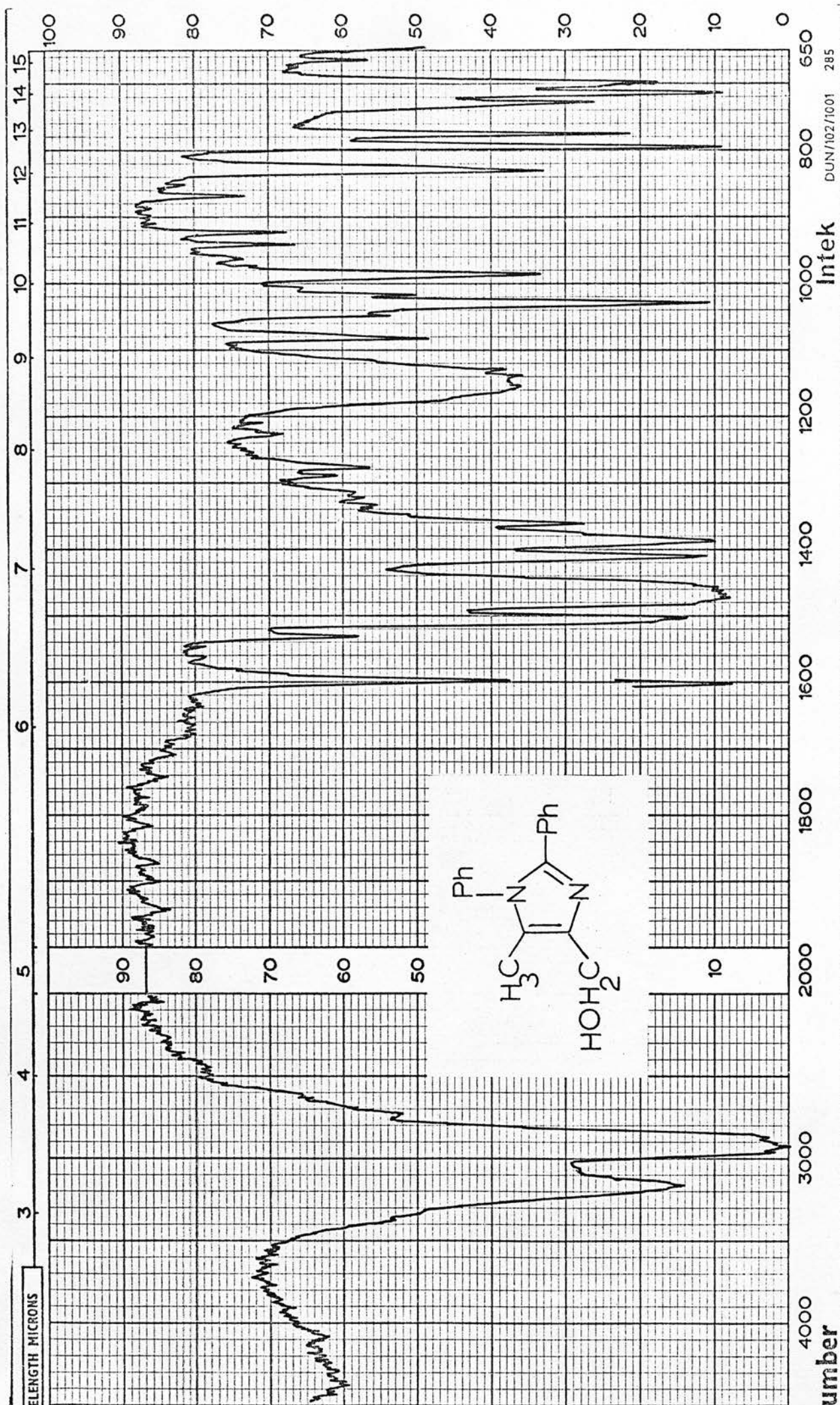
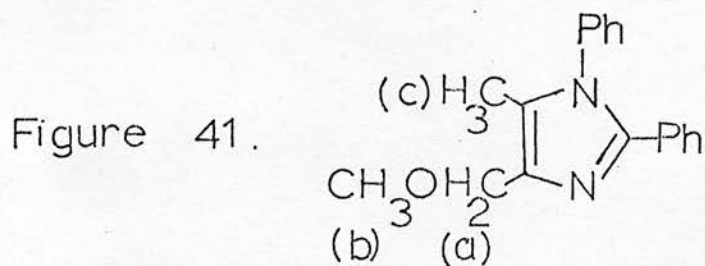
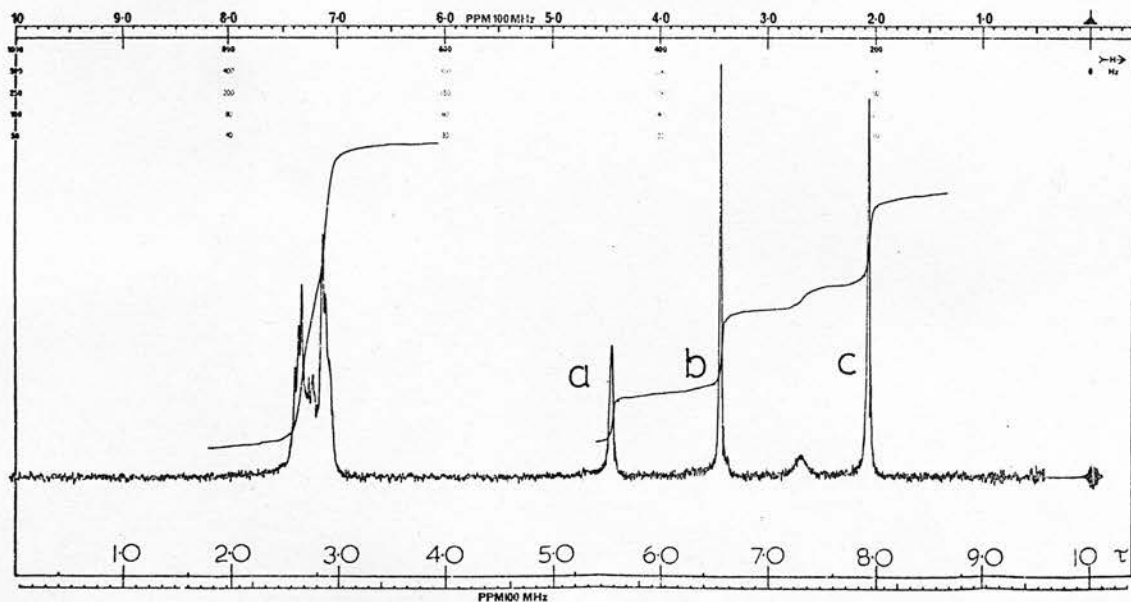
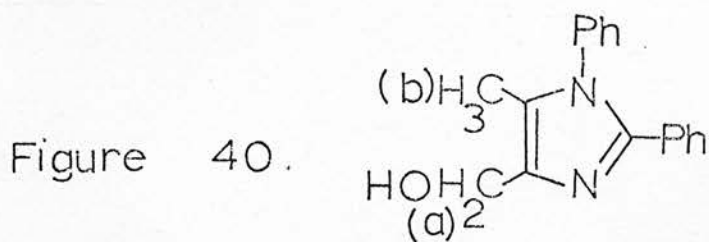
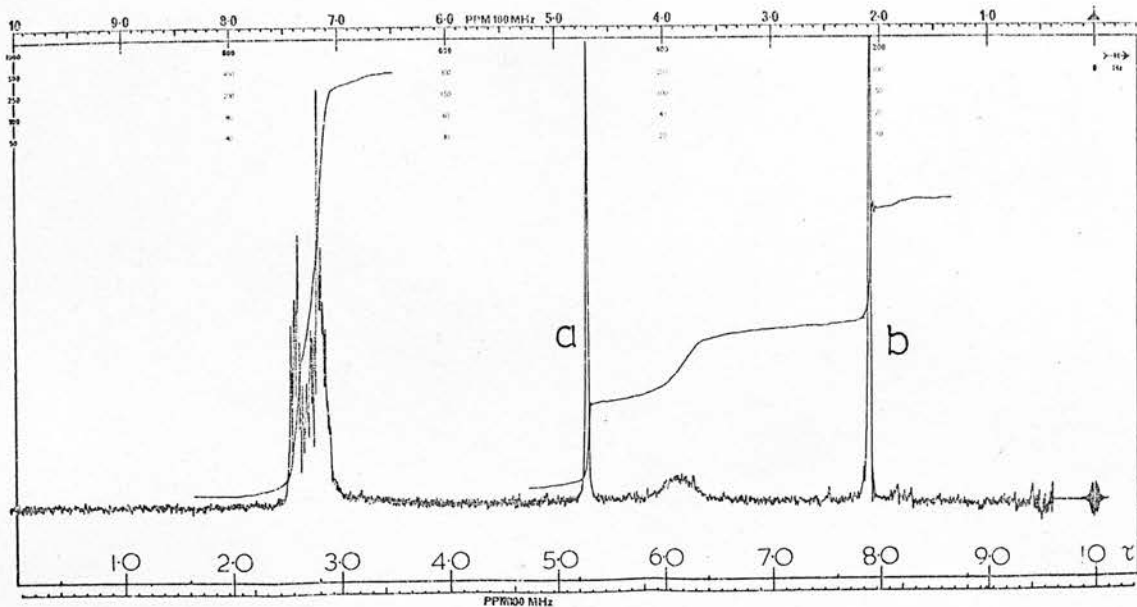


Figure 39.

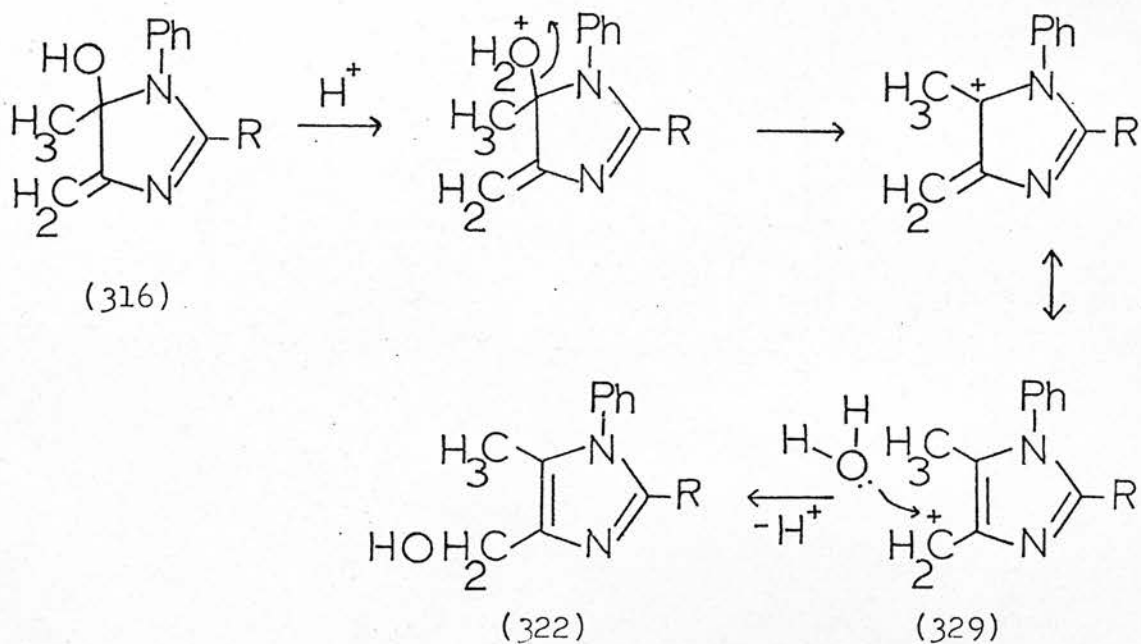
heating N-phenylbenzamidine with acetoin in ethanol, was unsuccessful.

The alkaline hydrolysis of the adduct (315a) or (316a) was carried out to see if further information on the structure could be obtained. No reaction occurred on leaving the adduct in contact with 10% aqueous sodium hydroxide in ethanol at room temperature for 24h. Heating under reflux in this medium for 30 min., however, caused complete degradation to a mixture of benzanilide, aniline and benzoic acid. In contrast, heating under reflux with N aqueous sodium carbonate had no effect on the adduct. This behaviour again tended to favour the structure (316a) as it is unlikely that the imino-ether (315a) would be stable to these basic conditions. On the other hand, degradation was too complete to afford positive evidence for the structure of the adduct.

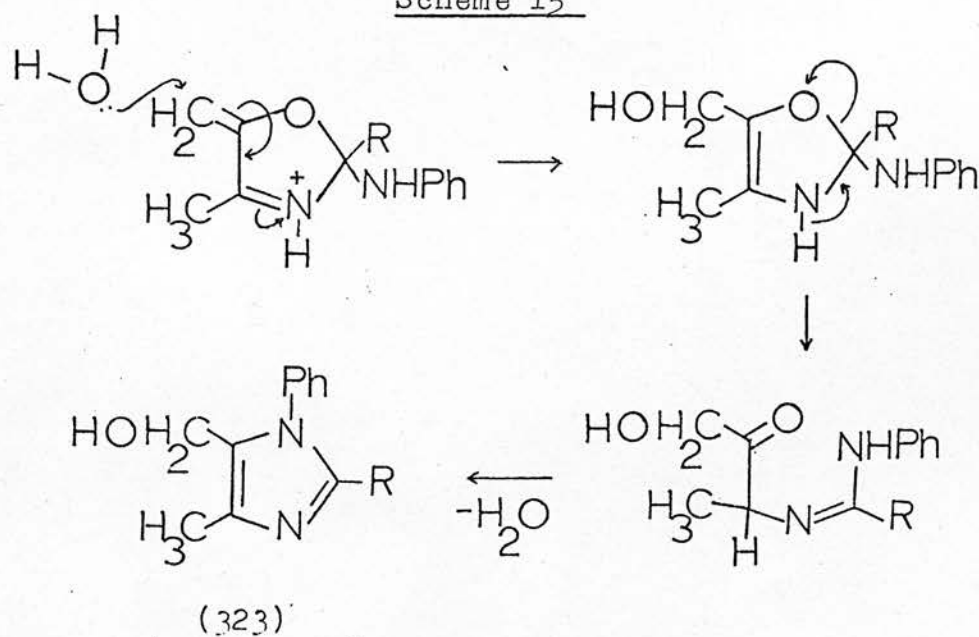
On warming for 30 min, with dilute sulphuric acid, the adduct (315a) or (316a) afforded an isomeric compound in high yield. Examination of the i.r. spectrum (Figure 39) and the ^1H n.m.r. spectrum (Figure 40 and Table 9) of this product indicated the presence of a hydroxymethyl group. This facile rearrangement can be readily explained, therefore, in terms of a simple allylic rearrangement of the imidazole derivative (316a) to the hydroxymethyl derivative (322a) (Scheme 14).



¹H n.m.r. spectra of compounds (322a)(Figure 40) and (327a)(Figure 41) at 100 MHz in deuteriochloroform.

Scheme 14

Alternatively a similar product (323a) could possibly be formed as shown in Scheme 15, from the Δ^4 -oxazoline structure (315a).

Scheme 15

The key difference between the possible products of rearrangement is that (322a) possesses a 4-hydroxymethyl-group whereas (323a) possesses a 5-hydroxymethyl-group. Unambiguous synthesis of either of the hydroxymethyl compounds (322a) or (323a) would therefore resolve the question of the structure of the product obtained from the N-oxide (30la) and phenyl isocyanate. While this approach was being considered, a paper was published by Goto et al.¹⁸⁷ in which they described the reaction of several oxazole 3-N-oxides with phenyl isocyanate and the subsequent acid-catalysed rearrangements and catalytic hydrogenation of the products obtained. The results obtained by Goto et al.¹⁸⁷ are in agreement with those obtained in the present study. These workers did not consider the possibility of the alternative structure (315). However this structure is excluded by the report by Goto et al.¹⁸⁷ that 5-ethyl-4-methyl-2-phenyloxazole 3-N-oxide (30lk) reacts with phenyl isocyanate to give a product (324) still containing an ethyl group. This means that in the case of the N-oxide (30la) the 5-methyl group cannot be involved in the formation of the adduct. Consequently the structure (315a) for the adduct and (319) and (323a) for the hydrogenation product and hydroxymethyl compound are excluded. Consequently, as also proposed by Goto et al.¹⁸⁷ the product obtained by reaction of the N-oxide (30la) with phenyl isocyanate is the 4-methylene-4,5-dihydroimidazole (316a) which on treatment with acid isomerises to the 4-hydroxymethyl-imidazole (322a). It also follows that the structure (320) is correct for the hydrogenation product of the adduct

derived from (301a). The synthesis of 4,5-dimethyl-1,2-diphenylimidazole (321) described by Goto et al.¹⁸⁷ was repeated with a slight modification, to confirm that this compound was identical with the product obtained by catalytic hydrogenation of (316a) and subsequent dehydration (see before).

In addition to the 2-p-anisyl-N-oxide (301c) which is known^{181,183} to react with phenyl isocyanate, the 2-p-chlorophenyl and 2-p-tolyl-N-oxides (301b) and (301d) were also found to react in the same way. The i.r. spectra and ¹H n.m.r. spectra (Table 8) of these products were very similar to those of the imidazole derivative (316a) and are thus assigned the structures (316b-d) by analogy. However, no such addition was found to occur with 2-aryloxazole-3-N-oxides possessing strongly electron-donating or electron-withdrawing substituents in the 2-aryl group even when the reaction mixtures were heated under reflux. This lack of reactivity appears to be independent of the position of the electron-donating or electron-withdrawing substituent. Thus the o-hydroxyphenyl- and p-N,N-dimethylaminophenyl N-oxides (301e) and (301f) failed to react but so also did both the m- and p-nitrophenyl N-oxides (301g) and (301h).

The possible mechanism for the reaction of phenyl isocyanate with the oxazole 3-N-oxides (301) is shown in Scheme 13. This mechanism is also suggested by Goto et al.¹⁸⁷ It is known that oxazoles can be converted into imidazoles because of the masked carbonyl properties of the ring oxygen atom of the oxazole structure. However the recyclisation of the postulated intermediate (328) (see

Scheme 13) is rather unusual. An attempt was made to synthesise this intermediate by treating biacetyl with N-phenylbenzamidine under conditions known to effect the condensation of amidines with carbonyl compounds. However, under the reaction conditions employed no condensation occurred.

The attempted extension of 1,3-dipolar cycloaddition reactions of oxazole 3-N-oxides to other dipolarophiles met with mixed success. 4,5-Dimethyl-2-phenyloxazole 3-N-oxide (301a) reacted readily with *p*-chlorophenyl isocyanate to give a product whose i.r. spectrum and ^1H n.m.r. spectrum (Table 8) were very similar to those of the product (316a) obtained from phenyl isocyanate. This product was also isomeric with that obtained from the N-oxide (301b) and phenyl isocyanate and is thus assigned the structure (325). However 4,5-dimethyl-2-phenyloxazole 3-N-oxide (301a) was recovered unchanged on treatment with methyl isocyanate at room temperature. When the reaction mixture was heated under reflux a gum was obtained which could not be solidified and which was shown by its ^1H n.m.r. spectrum to consist of several components. No attempt was made to separate this mixture. Reaction of the N-oxide (301a) with phenyl isothiocyanate might have been expected to yield the adduct (316a), also, but only a multi-component oil was obtained.

The allylic rearrangement of the adduct (316a) to the hydroxymethyl derivative (322a) was shown to occur also for the adducts (316b-d) and (325) affording the corresponding hydroxymethyl derivatives (322b-d) and (326). This

rearrangement was shown not to be restricted to treatment with aqueous acid. When the imidazole derivative (316a) was warmed in glacial acetic acid in the presence of concentrated sulphuric acid a product was isolated which was identical with that obtained by warming the hydroxymethyl compound (322a) with acetic anhydride. This product is thus formulated as the acetoxymethyl derivative (327a) which presumably arises by attack of acetic acid on the allylic carbonium ion (329) (See Scheme 14). Similarly, heating with methanol in the presence of acid afforded a product with no hydroxyl absorption in its i.r. spectrum and a methyl signal at τ 6.30 in its ^1H n.m.r. spectrum (Figure 41 and Table 9). On the basis of this evidence this product is assigned the structure (327b). Since no reaction occurred on heating the hydroxymethyl derivative (322a) with methanol and concentrated sulphuric acid, formation of the methoxy-derivative (327b) does not arise from the alcohol (322a). This latter control reaction excludes the possibility of rearrangement followed by methylation in the reaction medium. However the corresponding ethyl ether (327c) was not obtained by heating with ethanol and acid. The sole product of this reaction, obtained in low yield, was the hydroxymethylimidazole (322a).

PART THREE

EXPERIMENTAL

NOTES

Infrared spectra were measured for nujol suspensions using a Pye-Unicam SP 200 Spectrophotometer; bands were either strong or very strong, unless otherwise specified (w) as weak or (br) broad.

Nuclear magnetic resonance spectra were measured at 100 MHz using a Varian HA 100 instrument.

Mass spectra were measured at 800 Kv on an A.E.I. MS 902 instrument.

Microanalyses were carried out by Alfred Bernhardt, West Germany and by Mr. Brian Clark, Department of Chemistry, Edinburgh University. Melting points (uncorrected) of all analytical samples were determined on a Kofler-block.

Solvents were of technical grade unless otherwise specified and light petroleum had b.p. 60 - 80°C.

Recovery in chloroform refers to extraction, drying (MgSO_4) and evaporation under reduced pressure.

Alumina was Spence type H.

SECTION ONE

1.1. Preparation of 3-Aminobenzo-1,2,4-triazine
1-N-Oxides (161).

A mixture of the o-nitroaniline derivative (0.072 mol) and cyanamide (20.0g, 0.144 mol) was warmed at 100° giving a melt which was cooled to room temperature, treated with concentrated hydrochloric acid (25.0 ml), and warmed briefly at 100° until a vigorous reaction occurred. After cooling to room temperature the mixture was treated with a solution of sodium hydroxide (20.0g) in water (25.0 ml) and warmed at 100° for 0.5h. The yellow solid which separated on cooling and dilution with water was collected and crystallised from acetic acid to yield the 1-N-oxide (161). (¹H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a).

o-Nitroaniline gave compound (161a), (80%), as a yellow powder, m.p. 275° (lit.,¹²³ 271°) (from acetic acid), ν_{\max} . 3250 and 3100 (NH), 1655 and 1555 cm⁻¹.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 1-N-oxide (161b).

2-Nitro-p-toluidine gave compound (161b), (66%), as yellow platelets, m.p. 279° (lit.,¹¹⁷ 271°) (from acetic acid-water), ν_{\max} . 3350 and 3150 (NH), 1645 and 1550 cm⁻¹.

Found: C, 54.3%; H, 4.6%; N, 31.8%; M⁺, 176

C₈H₈N₄O requires: C, 54.5%; H, 4.5%; N, 31.8%; M, 176.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine 1-N-oxide (161c).

4-Amino-3-nitroanisole gave compound (161c), (91%), as a yellow powder, m.p. 273° (lit.,¹²³ 278-281°) (from acetic acid), ν_{\max} . 3300 and 3100 (NH), 1645 and 1550 cm⁻¹.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine 1-N-oxide (161d).

4-Chloro-2-nitroaniline gave compound (161d), (39%), as a yellow powder, m.p. $309-12^{\circ}$ (lit.,¹¹⁷ $302-5^{\circ}$) (from acetic acid), ν_{\max} . 3350 and 3150 (NH), 1650 and 1560 cm^{-1} .

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 1-N-oxide (161e).

4,5-Dimethyl-2-nitroaniline gave compound (161e), (75%), as a yellow powder, m.p. 288° (decomp.) (from acetic acid), ν_{\max} . 3375 and 3175 (NH), 1645 and 1545 cm^{-1} .

Found: C, 56.3%; H, 5.3%; N, 29.1%; M^+ , 190

$C_9H_{10}N_4O$ requires: C, 56.8%; H, 5.3%; N, 29.5%; M, 190.

1.2. Preparation of 3-Aminobenzo-1,2,4-triazines (162).

The 3-aminobenzo-1,2,4-triazine 1-N-oxide (161) (0.005 mol) was heated under reflux with twice its weight of sodium dithionite (added in two portions, the second portion after one hour) in 70% (v/v) aqueous ethanol (80.0 ml) for 2h. Hot filtration and concentration of the reaction mixture yielded a solid which was washed with water, dried and crystallised from ethanol or acetic acid to give the benzotriazine derivative (162), ν_{\max} . 3300 - 3250 and 3150 - 3125 (NH), 1670 - 1660 and $1560 - 1540\text{ cm}^{-1}$. (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine (162a) was obtained, (65%), as a yellow solid, m.p. 207° (lit.,¹²² 207°) (from ethanol). [Reduction of the N-oxide (161a) with zinc dust and glacial acetic acid¹²⁵ afforded compound (162a) (66%), m.p. 207° (lit.,^{122,125} 207° ; 211.5°).]

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine (162b) was obtained (87%), as a yellow solid, m.p. 227° (lit.,¹¹⁷ 218°) (from

acetic acid-water).

Found: C, 59.8%; H, 4.9%; N, 35.1%; M^+ , 160.
 $C_8H_8N_4$ requires: C, 60.0%; H, 5.0%; N, 35.0%; M, 160.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine (162c) was obtained, (84%), as yellow needles, m.p. 226° (lit.,¹¹⁷ 220°) (from acetic acid-water).

Found: C, 54.4%; H, 4.5%; N, 32.0%.
 $C_8H_8N_4O$ requires: C, 54.5%; H, 4.5%; N, 31.8%.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine (162d) was obtained, (73%), as a yellow solid, m.p. $252-5^\circ$ (lit.,¹¹⁷ 255°) (from acetic acid).

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine (162e) was obtained, (80%), as a yellow solid, m.p. 286° (decomp.) (from acetic acid).

Found: C, 61.5%; H, 5.7%; N, 31.7%; M^+ , 174.
 $C_9H_{10}N_4$ requires: C, 62.1%; H, 5.7%; N, 32.2%; M, 174.

1.3. Preparation of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxides (163).

A suspension of the 3-aminobenzo-1,2,4-triazine 1-N-oxide (161) (0.005 mol) in acetic acid (28 - 180 ml) was stirred and heated at $45-50^\circ$ for 18 - 60h with 30% aqueous hydrogen peroxide (11.5 - 45.0 ml). The suspended solid slowly dissolved giving a clear red solution. The mixture was treated with solid sodium bicarbonate to yield a red solid which was combined with material recovered by extracting the aqueous mother-liquors with chloroform, and crystallised from acetic acid-water to give the pure di-N-oxide (163). (1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a).

Oxidation in acetic acid (32.5 ml) with hydrogen peroxide (11.5 ml) for 18h gave compound (163a) as red plates, (89%), m.p. 219.5° (decomp.) [lit.,¹²⁷ 230° (decomp.)] (from acetic acid), ν_{\max} . 3350, 3200 and 3025 (NH), and 1630cm^{-1} .

Found: C, 46.7%; H, 3.3%; N, 31.8%; M^{+} , 178.

$C_7H_6N_4O_2$ requires: C, 47.2%; H, 3.4%; N, 31.5%; M, 178.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 1,4-di-N-oxide (163b).

Oxidation in acetic acid (36.0 ml) with hydrogen peroxide (13.5 ml) for 18h gave compound (163b) as red needles, (71%), m.p. 220° (decomp.) (from acetic acid-water), ν_{\max} . 3400, 3275 and 3100 (NH), and 1600cm^{-1} .

Found: C, 50.2%; H, 4.2%; N, 29.3%; M^{+} , 192.

$C_8H_8N_4O_2$ requires: C, 50.0%; H, 4.2%; N, 29.2%; M, 192.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine 1,4-di-N-oxide (163c).

Oxidation in acetic acid (28.0 ml) with hydrogen peroxide (13.5 ml) for 43h gave compound (163c) as orange needles, (73%), m.p. 225° [lit.,¹²⁷ $213-4^{\circ}$ (decomp.)] (from methanol)] (from acetic acid-water), ν_{\max} . 3425, 3300 and 3200 (NH), and 1620cm^{-1} .

Found: C, 45.3%; H, 3.9%; N, 26.7%.

$C_8H_8N_4O_3$ requires: C, 46.2%; H, 3.8%; N, 26.9%.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine 1,4-di-N-oxide (163d).

Oxidation in acetic acid (180 ml) with hydrogen peroxide (45.0 ml) for 18h gave compound (163d) as a red solid, (62%), m.p. 269° (decomp.) [lit.,¹²⁷ 295° (decomp.)] (from acetic acid-water), ν_{\max} . 3400, 3250 and 3025 (NH), and 1600cm^{-1} .

Found: C, 39.3%; H, 2.6%; N, 26.1%.

$C_{7.5}H_{5.4}ClN_4O_2$ requires: C, 39.4%; H, 2.5%; N, 26.3%.

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 1,4-di-N-oxide (163e).

Oxidation in acetic acid (24.0 ml) with hydrogen peroxide (12.0 ml) for 20h, followed by the addition of fresh acetic acid (8.0 ml) and hydrogen peroxide (4.0 ml) and the oxidation continued for a further 40h gave compound (163e) as red needles, (74%), m.p. 242° (decomp.) (from acetic acid-water), ν_{\max} . 3400, 3250 and 3200 (NH), and 1610 cm^{-1} .

Found: C, 51.7%; H, 5.0%; N, 26.7%; M^+ , 206.

$C_{9.5}H_{10.4}N_4O_2$ requires: C, 52.4%; H, 4.9%; N, 27.2%; M, 206.

1.4. Reaction of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxide (163a) with Sodium Dithionite.

The di-N-oxide (163a) heated under reflux with sodium dithionite in 70% (v/v) aqueous ethanol for 20 min, as above, afforded 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a), (50%), m.p. 275° (lit.,¹²⁷ 271°), identical (mixed m.p. and i.r. spectrum) with an authentic sample.

1.5. Reaction of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxides (163) with Acetic Anhydride.

The di-N-oxides (163) were warmed with acetic anhydride for 1 min to give the corresponding monoacetyl derivatives (164), ν_{\max} . 3300-3225 (NH), 1720 (CO) and $1555\text{--}1540\text{ cm}^{-1}$. (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Acetylaminobenzo-1,2,4-triazine 1,4-di-N-oxide (164a) was obtained as yellow needles, (77%), m.p. 190° (from ethanol).

Found: C, 49.2%; H, 3.6%; N, 25.6%; M^+ , 220.

$C_9H_8N_4O_3$ requires: C, 49.1%; H, 3.6%; N, 25.5%; M, 220.

(ii) 3-Acetylamino-7-methylbenzo-1,2,4-triazine 1,4-di-N-oxide (164b) was obtained as an orange solid, (69%), m.p. 212° (from acetic acid-water).

Found: C, 51.3%; H, 4.4%; N, 23.9%; M^+ , 234.

$C_{10}H_{10}N_4O_3$ requires: C, 51.3%; H, 4.3%; N, 23.9%; M, 234.

(iii) 3-Acetylamino-7-methoxybenzo-1,2,4-triazine 1,4-di-N-oxide (164c) was obtained as orange needles, (80%), m.p. 219° (from acetic acid-water).

Found: C, 48.6%; H, 4.0%; N, 22.0%.

$C_{10}H_{10}N_4O_4$ requires: C, 48.0%; H, 4.0%; N, 22.4%.

(iv) 3-Acetylamino-7-chlorobenzo-1,2,4-triazine 1,4-di-N-oxide (164d) was obtained as an orange solid, (77%), m.p. 213° (from acetic acid-water).

Found: C, 42.5%; H, 2.8%; N, 22.1%.

$C_9H_7ClN_4O_3$ requires: C, 42.3%; H, 2.8%; N, 22.0%.

(v) 3-Acetylamino-6,7-dimethylbenzo-1,2,4-triazine 1,4-di-N-oxide (164e) was obtained as a yellow solid, (83%), m.p. 197° (from ethanol).

Found: C, 52.9%; H, 4.8%; N, 22.5%; M^+ , 248.

$C_{11}H_{12}N_4O_3$ requires: C, 53.2%; H, 4.8%; N, 22.6%; M, 248.

1.6. Preparation of 3-Aminobenzo-1,2,4-triazine 2-N-Oxides (165).

(a) A suspension of the 3-aminobenzo-1,2,4-triazine (162a), (162b) or (162e) (0.003 mol) in glacial acetic acid (8-12 ml) was stirred at room temperature for 46h with 30% aqueous

hydrogen peroxide (8.0 ml). The insoluble solid was collected, combined with material obtained by neutralising the filtrate with solid sodium bicarbonate and crystallised from acetic acid to give the corresponding 2-N-oxides, (165a), (165b) or (165e). (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 2-N-oxide (165a) was obtained as yellow needles, (46%), m.p. 200° (lit.,¹²⁴ 187°) (from acetic acid-water), ν_{max} . 3400 and 3200-3100 br(NH), and 1680 cm^{-1} .

Found: C, 51.3%; H, 3.6%; N, 34.6%; M^+ , 162.

$\text{C}_7\text{H}_6\text{N}_4\text{O}$ requires: C, 51.8%; H, 3.7%; N, 34.6%; M, 162.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 2-N-oxide (165b) was obtained as a yellow solid, (76%), m.p. 203° (from acetic acid-water), ν_{max} . 3400 and 3200-3100 br(NH), and 1680 cm^{-1} .

Found: C, 54.6%; H, 4.5%; N, 31.5%; M^+ , 176.

$\text{C}_8\text{H}_8\text{N}_4\text{O}$ requires: C, 54.5%; H, 4.5%; N, 31.8%; M, 176.

(iii) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 2-N-oxide (165e) was obtained as a yellow solid, (91%), m.p. 226° (from acetic acid), ν_{max} . 3400 and 3150 (NH), and 1675 cm^{-1} .

Found: C, 57.3%; H, 5.4%; N, 29.6%; M^+ , 190.

$\text{C}_9\text{H}_{10}\text{N}_4\text{O}$ requires: C, 56.8%; H, 5.3%; N, 29.5%; M, 190.

(b) Alternatively the 3-aminobenzo-1,2,4-triazines (162c) or (162d) in glacial acetic acid were treated at room temperature for 80h with 30% aqueous hydrogen peroxide, as in (a) above, and the crude product was crystallised to give the 2-N-oxides (165c) or (165d) (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Amino-7-methoxybenzo-1,2,4-triazine 2-N-oxide (165c) was obtained as yellow needles, (47%), m.p. 194° [lit.,¹²⁷ 183° (decomp.) (from methanol)] (from acetic acid-water), ν_{\max} . 3400 and 3200-3100 br (NH), and 1680 cm^{-1} .

Found: C, 50.2%; H, 4.4%; N, 29.1%.

$\text{C}_8\text{H}_8\text{N}_4\text{O}_2$ requires: C, 50.0%; H, 4.2%; N, 29.2%.

(ii) 3-Amino-7-chlorobenzo-1,2,4-triazine 2-N-oxide (165d) was obtained as a yellow solid, (74%), m.p. 223° (lit.,¹²⁷ 215°) (from acetic acid-water), ν_{\max} . 3400 and 3100 (NH), and 1680 cm^{-1} .

Found: C, 42.7%; H, 2.6%; N, 28.5%.

$\text{C}_7\text{H}_5\text{ClN}_4\text{O}$ requires: C, 42.7%; H, 2.5%; N, 28.5%.

1.7. Peracid Oxidation of 3-Aminobenzo-1,2,4-triazine (162a) at 50° .

(a) A suspension of 3-aminobenzo-1,2,4-triazine (162a) (0.25g) in glacial acetic acid (6.0 ml) was stirred and heated at $45 - 50^{\circ}$ for 3h with 30% aqueous hydrogen peroxide (2.0 ml). The red solution was neutralised with solid sodium bicarbonate. The precipitate was filtered and combined with material obtained by chloroform extraction of the filtrate, to afford 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a), (70%), identical (m.p. and i.r. spectrum) with an authentic sample.

(b) Repetition of the oxidation described in (a) for 17h afforded a red solution. Dilution with water and neutralisation of the reaction mixture with solid sodium bicarbonate yielded no precipitate. Constant chloroform extraction afforded

3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a), (41%), identical (m.p. and i.r. spectrum) with an authentic sample.

1.8. Peracid Oxidation of 3-Aminobenzo-1,2,4-triazine 2-N-Oxide (165a) at 50°.

A suspension of 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a) (0.2g) in glacial acetic acid (8.0 ml) was stirred and heated at 45 - 50° for 22h with 30% aqueous hydrogen peroxide (3.0 ml). Neutralisation of the red solution with solid sodium bicarbonate afforded no precipitate. Constant chloroform extraction yielded a red gummy solid, which on trituration with ether gave 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a), (36%), identical (m.p. and i.r. spectrum) with an authentic sample.

1.9. Attempted Isomerisation of the 2-N-Oxide (165a) into the 1-N-Oxide (161a) with Perchloric Acid.

A suspension of 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a) (0.1g) in glacial acetic acid (5.0 ml) was treated with perchloric acid (3 drops) and stirred and heated at 45 - 50° for 17h. The yellow solid was filtered and stirred with saturated sodium bicarbonate solution for 30 min. Filtration afforded unchanged starting 2-N-oxide (165a).

1.10. Oxidation of 3-Phenylbenzo-1,2,4-triazine (169).

(a) 3-Phenylbenzo-1,2,4-triazine (169) was prepared by cyclisation¹³⁶ of 1,3,5-triphenylformazan (157; Ar=Ph).¹⁸⁸

(b) 3-Phenylbenzo-1,2,4-triazine 1-N-oxide (170).¹²⁷

(i) A solution of 3-phenylbenzo-1,2,4-triazine (169) (0.5g) in glacial acetic acid (8.0 ml) was stirred and heated at 45 - 50° for 20h with 30% aqueous hydrogen peroxide (3.0 ml). The reaction mixture was cooled affording an orange solid which was combined with material obtained by dilution of the mother liquors with water, giving compound (170), (75%), m.p. 131° (lit.,¹²⁷ 133°), T.L.C. in benzene-ether over silica showed one spot.

(ii) Similarly, oxidation at room temperature for 2 days or 7 days afforded a product in 80% and 85% yield respectively, identical (m.p., mixed m.p., i.r. spectra and T.L.C.) with compound (170). [Robbins and Schofield¹²⁷ obtained 3-phenylbenzo-1,2,4-triazine 2-N-oxide (171) from this treatment, and found that further oxidation at 45 - 50° for 40h converted the 2-N-oxide (171) into 3-phenylbenzo-1,2,4-triazine 1-N-oxide (170).]

1.11. Electrophilic Substitution of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

(a) Nitration of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

Nitration of 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a) by the method of Robbins and Schofield¹²⁷ afforded 3-amino-7-nitrobenzo-1,2,4-triazine 1-N-oxide (172), (84%), m.p. 249° (from glacial acetic acid)[lit.,^{127,134} 289° (decomp.) (from dioxan)], ν_{\max} . 3350 (NH), 1695, 1670 and 1620 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.76 (1 H, d, J 9.0 Hz, H - 8), 1.12 (1 H, dd, J_o 9.0 Hz, J_m 2.25 Hz, H - 6) and 1.95 (1 H, d, J 2.25 Hz, H - 5), M^+ , 207 (M, 207).

(b) Attempted Bromination of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a) (0.65g) was dissolved in glacial acetic acid (80.0 ml) and stirred in an ice-bath. Bromine in glacial acetic acid (0.4 ml of a solution of 10.75g bromine made up to 10.0 ml with glacial acetic acid) was added dropwise giving a red solution. Stirring was continued in the ice-bath for 15 min and then at room temperature for 15 min. Dilution with water afforded the starting N-oxide (161a) (92% recovery).

1.12. Attempted Alkylation of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a) with Methyl Iodide.

3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a) (0.5g) was suspended in acetonitrile (23.0 ml) and stirred in the dark for 20h with methyl iodide (1.0 ml) and then in daylight for a further 7h. Filtration gave the starting N-oxide (161a) (88% recovery).

1.13. Attempted Photochemical Rearrangement of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

Irradiation of 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a) (1.5g) in dimethylformamide (200 ml) for 24h afforded the starting N-oxide (161a) (71% recovery).

1.14. Attempted Preparation of 4-Hydroxybenzo-1,2,4-triazine-3(4H)-one 1-N-Oxide (175).

(a) Attempted Diazotisation of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxide (163a).

(i) A solution of 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide

(163a) (0.1g) in 50% (w/v) aqueous sulphuric acid (5.0 ml) was cooled to 0° and treated in portions with solid sodium nitrite (0.06g). The mixture was left at 0° for 5 min then at room temperature for 15 min and poured into water (40 ml). The pH of the solution was adjusted to 6 by the addition of 10% aqueous sodium hydroxide and the reaction mixture was extracted with chloroform. The dried (MgSO_4) chloroform extract was evaporated to afford the starting di-N-oxide (163a) (0.035g, 35%).

(ii) A solution of 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a) (0.1g) in 70% (v/v) aqueous acetic acid (5.0 ml) was cooled to 0° and solid sodium nitrite (0.06g) was added with swirling. The mixture was left at 0° for 5 min, at room temperature for 15 min and then heated under reflux for 1.25h. Evaporation of the acetic acid under reduced pressure afforded the starting di-N-oxide (163a) (0.09g, 90%).

(b) Attempted Oxidation of Benzo-1,2,4-triazin-3(4H)-one 1-N-Oxide (176).

(i) Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176)¹²³ was obtained (78%) by diazotising 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a). It had m.p. 220° (from glacial acetic acid) (lit.,¹²² 219°). [Jiu and Mueller¹²³ report m.p. 242-6° (from methanol)].

(ii) A suspension of benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (0.25g) in glacial acetic acid (7.0 ml) was stirred at 45 - 50° for 19h with 30% aqueous hydrogen peroxide (4.0 ml). Filtration of the mixture afforded the starting N-oxide (176), (0.105g, 42%). No further material was obtained either by

dilution or by neutralisation with solid sodium bicarbonate and extraction with chloroform.

(c) Attempted Oxidation of 3-Chlorobenzo-1,2,4-triazine 1-N-Oxide (177) and 3-Methoxybenzo-1,2,4-triazine 1-N-oxide (178).

(i)(a) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177).

Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) was heated under reflux in excess of phosphorus oxychloride for 2h¹²³ giving 3-chloro-benzo-1,2,4-triazine 1-N-oxide (177) (60%), together with starting material (17%).

(b) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (0.9g) was stirred in glacial acetic acid (25.0 ml) with 30% aqueous hydrogen peroxide (12.0 ml) at 45 - 50° for 48h. The reaction mixture was diluted with water and extracted with chloroform to give unreacted starting N-oxide (0.5g, 55%).

(c) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (0.9g) was stirred in glacial acetic acid (25.0 ml) with 30% aqueous hydrogen peroxide (12.0 ml) at 65° for 17h then at 80° for 2h to give a yellow solution. The reaction mixture was cooled, diluted with water and neutralised with solid sodium bicarbonate to give a yellow precipitate (0.84g). The product was washed with chloroform leaving a residue, (0.55g, 67%) identical (m.p. and i.r. spectrum) with benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176). Evaporation of the chloroform washings afforded unreacted starting material (0.29g, 33%).

(ii) (a) 3-Methoxybenzo-1,2,4-triazine 1-N-oxide (178).

3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (3.6g) was dissolved in methanol (25.0 ml) with heating. A solution of sodium (0.8g) in methanol (35.0 ml) was added and the reaction mixture was heated under reflux for 1h. The mixture was filtered hot to remove sodium chloride and the filtrate on cooling afforded a pale yellow solid (2.1g). This was combined with material obtained by evaporating the filtrate and washing the residue with water, (0.62g), giving 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178), (2.72g, 77%), as pale yellow needles, m.p. 120° (from methanol), ν_{\max} . 1590 and 1550 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.84 (4H, m, Ar-H) and 5.54 (3H, s, OCH_3).

Found: C, 54.3%; H, 4.0%; N, 23.9%.

$\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ requires: C, 54.2%; H, 4.0%; N, 23.7%.

Acidification of the aqueous washings with dilute hydrochloric acid afforded benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (0.35g, 10%).

(b) A solution of 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178) (0.8g) in glacial acetic acid (15.0 ml) was stirred at $45-50^{\circ}$ for 66h with 30% aqueous hydrogen peroxide (10.0 ml). More hydrogen peroxide (10.0 ml) was added and stirring was continued for a further 6h. The dark yellow solution was diluted with water and neutralised with solid sodium bicarbonate giving the starting N-oxide (178) (0.51g, 64%).

(c) A solution of 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178) (0.8g) in glacial acetic acid (15.0 ml) was stirred at

80° for 24h with 30% aqueous hydrogen peroxide (10.0 ml) giving a dark red solution. On addition of more hydrogen peroxide (10.0 ml) the solution temporarily reverted to yellow with vigorous gas evolution. Stirring was continued for a further 20h and the dark red solution was diluted with water and neutralised with solid sodium bicarbonate. No precipitate was obtained but constant chloroform extraction afforded benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (14%) identical (m.p. and i.r. spectrum) with an authentic sample.

1.15. Attempted Reaction of 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-Oxide (179) with Acetic Anhydride.

(a) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179).

(i) Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (2.0g) was heated under reflux with anhydrous potassium carbonate (6.0g) in anhydrous acetone (150 ml). Dimethyl sulphate (4.0 ml) was added dropwise and heating was continued for 4h. The reaction mixture was evaporated under reduced pressure and the yellow residue was treated with water. Extraction into chloroform and evaporation of the dried (MgSO_4) extract gave compound (179), (60%), m.p. 229-232° (lit.,¹²³ 235.5 - 240°), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.52 (1H, dd, J_o 8.0 Hz, J_m 2.0 Hz, H - 8), 1.86 (1H, qd, H - 7), 2.22 (1H, dd, H - 5), 2.34 (1H, m, H - 6) and 6.04 (3H, s, N-CH₃), M^+ , 177 (M, 177).

(ii) N-Methyl-o-nitroaniline (2.19g) and cyanamide (1.21g) were fused on a water bath at 100°, then cooled to room temperature and treated with concentrated hydrochloric acid (5.0 ml). The reaction mixture was heated gently then

cooled to room temperature. Sodium hydroxide (4.0 g) in water (5.0 ml) was added and the reaction mixture was heated on a water bath for 0.5h. The orange solid which was obtained on cooling was combined with material obtained by dilution with water to give unreacted N-methyl-o-nitroaniline (recovery quantitative).

(b)(i) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179) (0.53g, 0.003 mol) heated under reflux in acetic anhydride (5.0 ml) for 2h or 7.5h gave the starting N-oxide (179) (recovery 93%) by filtration and evaporation of the reaction mixture.

(ii) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179) (0.53g, 0.003 mol) when heated under reflux with acetic anhydride (5.0 ml) and concentrated sulphuric acid (2 drops) for 0.25h gave a dark green solution. After cooling, filtration and extraction afforded the starting N-oxide (179) (85% recovery).

1.16. Attempted Reaction of 3-Acetylamino-1,2,4-triazine 1,4-Di-N-oxide (164a) with Concentrated Sulphuric Acid.

A solution of 3-acetylamino-1,2,4-triazine 1,4-di-N-oxide (164a) (0.002 mol) in concentrated sulphuric acid (5.0 ml) was stirred at room temperature for 20h. When ether (25.0 ml) was added and the reaction mixture was chilled, a hygroscopic yellow solid was precipitated. Addition of fluoroboric acid to an aqueous solution of the yellow solid failed to give a precipitate. In the presence of a little water the yellow solid was converted into the red 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a) (25%).

SECTION TWO

2.1. Preparation of Substituted o-Nitroanilines

(i) 4-Bromo-2-nitroaniline (195d)

o-Nitroaniline (27.6g, 0.2 mol) was dissolved in glacial acetic acid (420 ml) and the solution was cooled in ice. A solution of bromine (21.5g, 0.27 mol) made up to 20.0 ml with glacial acetic acid was added dropwise (1.0 - 1.5 ml/min) to the stirred solution. When the addition was complete the reaction mixture was diluted with water and the orange solid which precipitated as needles was filtered off and crystallised from ethanol-water to give 4-bromo-2-nitroaniline (195d) (72%), m.p. 108° (lit.,¹⁵⁷ 111.5°), ν_{\max} . 3450 and 3325 (NH) cm^{-1} .

Using Fuchs,¹⁵⁷ conditions, and adding the bromine solution dropwise or all at once, gave the yellow 4,6-dibromo-2-nitroaniline, m.p. 127° (from ethanol-water), (lit.,¹⁸⁹ 127°), ν_{\max} . 3425 and 3325 (NH) cm^{-1} , τ (CDCl_3) 1.75 (1H, d, J 2.4 Hz, H-3), 2.23 (1H, d, J 2.4 Hz, H-5), and 3.40 (2H, s, NH_2).

(ii) 4,5-Dimethyl-2-nitroaniline (207a).

Nitration¹⁹⁰ of 3,4-dimethylaniline afforded compound (207a) (50%), m.p. 140° (from ethanol) (lit.,¹⁹⁰ 140°), ν_{\max} . 3500 and 3400 (NH), and 1630 (NH) cm^{-1} .

(iii) 4,5-Dimethoxy-2-nitroaniline (207b).

(a) 4,5-Dinitroveratrole obtained (88%) by nitrating¹⁹¹ veratrole had m.p. 122-6° (lit.,¹⁹¹ 131°).

(b) Reduction of 4,5-dinitroveratrole with stannous chloride and ethanolic hydrochloric acid¹⁹² afforded compound (207b)

(75%), m.p. 166° (lit.,¹⁹² 170°), ν_{\max} . 3425 and 3300 (NH) and 1640 (NH) cm^{-1} .

2.2. Preparation of Benzofuroxans (196) and (208).

A series of benzofuroxans (196a-e) and (208a-b) were prepared according to the method of Mallory.¹⁵⁶

Potassium hydroxide (21.0g) and 95% ethanol (250 ml) were heated on a steam bath until solution was obtained. The o-nitroaniline derivative (0.3 mol) was dissolved in the warm ethanolic alkali and the red solution was cooled to 0° , stirred and treated dropwise over 0.5h with a freshly prepared solution of sodium hypochlorite [prepared by passing chlorine gas (41.0g) at 0° into a solution of sodium hydroxide (50.0g) in water (200 ml) containing crushed ice (100g)]. Stirring was continued until the red colour disappeared (1h). The precipitate was collected, washed with water (200 ml), air dried and crystallised to yield the benzofuroxans (196a-e) and (208a-b), ν_{\max} . 1620 and 1590 cm^{-1} .

(i) Benzofuroxan (196a) was obtained in quantitative yield, m.p. 68° (lit.,¹⁵⁶ 73°).

(ii) 5-Methylbenzofuroxan (196b) (91%), had m.p. 95° (lit.,¹⁹³ 98°).

(iii) 5-Methoxybenzofuroxan (196c) (77%), had m.p. 116° (lit.,¹⁹³ 118°).

(iv) 5-Bromobenzofuroxan (196d) (83%), had m.p. 65° (lit.,¹⁹⁴ 69°).

(v) 5-Chlorobenzofuroxan (196e) (90%), had m.p. 48° (lit.,¹⁹⁵ 48°).

(vi) 5,6-Dimethylbenzofuroxan (208a) was obtained in quantitative yield, and had m.p. 137° (lit.,¹⁹⁶ 139°).

(vii) 5,6-Dimethoxybenzofuroxan (208b) formed pink needles (62%), m.p. 221° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 3.04 (1H, s, H-4), 3.26 (1H, s, H-7), and 5.88 (6H, s, OCH_3 -5 and OCH_3 -6).

Found: C, 49.2%; H, 3.9%; N, 14.0%.

$\text{C}_8\text{H}_8\text{N}_2\text{O}_4$ requires: C, 49.0%; H, 4.1%; N, 14.3%.

2.3. Reactions of Benzofuroxans (196) with Active Methylene Compounds.

The benzofuroxan (196) (0.01 mol) and the active methylene compound (0.011 mol) were dissolved in ethanol (20.0 ml) with warming if necessary. Piperidine (1.0 ml) was added and the reaction mixture was stirred at room temperature for 24-72 h to ensure complete reaction. Filtration afforded the quinoxaline 1,4-di-N-oxides (189), (191), (193a) or (206). Working up the mother liquors gave no further product.

(i) 2-Acetyl-3-methylquinoxaline 1,4-di-N-oxide (189a) was obtained from acetylacetone, (50%), m.p. 151° (lit.,¹⁵⁰ 154°), ν_{max} . 1700 (CO) cm^{-1} , τ (CDCl_3) 1.35-1.50 (2H, m, H-5 and H-8), 2.05-2.20 (2H, m, H-6 and H-7), 7.30 (3H, s, COCH_3), and 7.50 (3H, s, CH_3). This product was also obtained (46%) m.p. 152° , by stirring the two reagents in triethylamine (8.0 ml) for 22h. The attempted reaction of benzofuroxan (196a) with acetylacetone using different reaction conditions was unsuccessful. The use of ethereal

hydrogen chloride, or acetic anhydride and solid sodium bicarbonate, as reaction medium, resulted in recovery of starting material (88% and 75% respectively). The use of sodium methoxide yielded a dark, uncharacterised solid.

(ii) 2-Acetyl-3,6-dimethylquinoxaline 1,4-di-N-oxide (206) was obtained from acetylacetone as pale, yellow needles (57%), m.p. 177° (from benzene-light petroleum), T.L.C. over silica in chloroform showed only one spot, ν_{\max} . 1720 (CO) cm^{-1} , τ (CDCl_3) 1.51 (1H, d, J 10.0 Hz, H-8), 1.66 (1H, s, H-5), 2.30 (1H, dd, J_m 2.0 Hz, J_o 10.0 Hz, H-7), 7.30 (3H, s, COCH_3), 7.40 (3H, s, CH_3), and 7.50 (3H, s, CH_3).

Found: C, 62.4%; H, 5.1%; N, 12.1%; M^+ , 232. $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 62.1%; H, 5.2%; N, 12.1%; M, 232.

(iii) 2-Benzoyl-3-methylquinoxaline 1,4-di-N-oxide (189b) was obtained from benzoylacetone as pale yellow needles, (51%), m.p. 211° (from ethanol-acetic acid), T.L.C. over silica in ether showed only one spot, ν_{\max} . 1680 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.10 - 2.44 (9H, m, Ar-H) and 7.19 (3H, s, CH_3).

Found: C, 68.9%; H, 4.4%; N, 9.5%. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 68.6%; H, 4.3%; N, 10.0%.

(iv) 3-Amino-2-cyanoquinoxaline 1,4-di-N-oxide (191a) was obtained from malononitrile, (82%), m.p. 238° (decomp.) [lit., 151 232° (decomp.)], ν_{\max} . 3375 and 3275 (NH), 2200 (CN), and 1630 cm^{-1} .

(v) 2-Cyano-4-hydroxyquinoxalin-3(4H)-one 1-N-oxide (193a).

Reaction of benzofuroxan (52; R=H) and ethyl cyanoacetate, as above, afforded a red solid in very poor yield (19%). Because of the similarity of its i.r. spectrum to that of the

ammonium salt obtained below, this red solid is assumed to be the piperidine salt of the N-oxide (193a).

Because of the very low yield, a different procedure was required to synthesise compound (193a).

The ethanol solution of the two reagents was saturated with ammonia gas and left stoppered at room temperature for 24h. The precipitated, red ammonium salt was dissolved in water and filtered to remove insoluble impurity. Acidification of the filtrate with glacial acetic acid afforded a by-product, $C_9H_7N_3O_4$, (14%), which was not characterised.

Found: C, 49.0%; H, 3.6%; N, 16.9%.

$C_9H_7N_3O_4$ requires: C, 48.9%; H, 3.2%; N, 19.0%.

The mother-liquors were evaporated under reduced pressure to give a red solid, which was triturated with dilute sulphuric acid to afford 2-cyano-4-hydroxyquinoxalin-3(4H)-one 1-N-oxide (193a), (24%), as yellow needles, m.p. 235° (from methanol), ν_{\max} . 3400 br(OH) and 1620 (CO) cm^{-1} , τ (CF_3CO_2H) 1.52 (1H, d, J 8.0 Hz, H-8), and 1.86-2.36 (3H, m, Ar-H).

Found: C, 53.1%; H, 2.7%; N, 20.9%; M^+ , 203.

$C_9H_5N_3O_3$ requires: C, 53.2%; H, 2.5%; N, 20.7%; M, 203.

2.4. Attempted Reaction of 2-Acetyl-3-methylquinoxaline 1,4-Di-N-oxide (189a) with Peracetic Acid.

(i) A solution of 2-acetyl-3-methylquinoxaline 1,4-di-N-oxide (189a) (0.22g) in glacial acetic acid (4.0 ml) was treated with 30% (v/v) aqueous hydrogen peroxide (1.0 ml) and the reaction mixture was stirred at room temperature for 17h.

The reaction mixture was diluted with water and concentrated under reduced pressure. Neutralisation with solid sodium bicarbonate, followed by chloroform extraction, afforded the starting N-oxide (0.15g, 68% recovery).

(ii) Heating under reflux for 17h caused decomposition and only a dark, intractable gum was obtained.

2.5. Preparation of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199) and (209).

Benzoylacetonitrile was prepared by the method of Gabriel and Eschenbach,¹⁹⁷ (quantitative yield), m.p. 79° (lit.,¹⁹⁷ 81°). The benzofuroxan (196) or (208) (0.1 mol) and benzoylacetonitrile (0.11 mol) were suspended in ethanol (450-750 ml) and the reaction mixture was saturated with ammonia gas. The resulting red solution, or suspension, was left stoppered at room temperature for 20h. The yellow solid which precipitated was collected and combined with material obtained by concentrating the mother-liquors and crystallised to give the pure di-N-oxide (199) or (209), ν_{\max} . 2250 (CN) and 1600 cm^{-1} , ^1H n.m.r. spectra, Table 4.

(i) 3-Cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) was obtained as yellow needles, (74%), m.p. 208° (from acetic acid-water).

Found: C, 68.2%; H, 3.6%; N, 16.2%.

$\text{C}_{15}\text{H}_9\text{N}_3\text{O}_2$ requires: C, 68.4%; H, 3.5%; N, 16.0%.

This product was also obtained by stirring the two reagents for 20h in (a) triethylamine (15.0 ml) (45% yield),
(b) dimethylformamide (6.0 ml) and piperidine (1.0 ml)

(71% yield), or (c) ethanol (20.0 ml) and piperidine (1.0 ml) (73% yield).

(ii) 3-Cyano-6-methyl-2-phenylquinoxaline 1,4-di-N-oxide (199b) was obtained as yellow plates, (62%; 91%, based on recovered starting material, isolated from the mother liquors), m.p. 211.5° (from acetic acid-water).

Found: C, 69.3%; H, 4.2%; N, 15.0%.

$C_{16}H_{11}N_3O_2$ requires: C, 69.3%; H, 4.0%; N, 15.2%.

(iii) 3-Cyano-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (199c) was obtained as yellow needles, (74%), m.p. 223° (from acetic acid-water).

Found: C, 65.8%; H, 4.1%; N, 14.2%.

$C_{16}H_{11}N_3O_3$ requires: C, 65.5%; H, 3.8%; N, 14.3%.

(iv) 6-Bromo-3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199d) was obtained as yellow needles, (60%), m.p. 216° (from acetic acid-water).

Found: C, 52.2%; H, 2.3%; N, 12.0%.

$C_{15}H_8BrN_3O_2$ requires: C, 52.6%; H, 2.3%; N, 12.3%.

(v) 6-Chloro-3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199e) was obtained as yellow plates, (75%), m.p. 218° (from glacial acetic acid).

Found: C, 60.4%; H, 2.7%; N, 14.2%.

$C_{15}H_8ClN_3O_2$ requires: C, 60.5%; H, 2.7%; N, 14.1%.

(vi) 3-Cyano-6,7-dimethylquinoxaline 1,4-di-N-oxide (209a) was obtained as yellow plates, (67%), m.p. 224° (from glacial acetic acid).

Found: C, 70.0%; H, 4.4%; N, 14.1%.

$C_{17}H_{13}N_3O_2$ requires: C, 70.1%; H, 4.5%; N, 14.4%.

(vii) 3-Cyano-6,7-dimethoxyquinoxaline 1,4-di-N-oxide (209b) prepared as above, was contaminated with 5,6-dimethoxybenzofuroxan (208b) and the two compounds could not be separated by crystallisation. A modified procedure was therefore used. A suspension of 5,6-dimethoxybenzofuroxan (0.1 mol) and benzoylacetonitrile (0.11 mol) in dimethylformamide (30.0 ml) was treated with piperidine (1.0 ml). The reaction mixture was stirred at room temperature for 2h and more piperidine (1.0 ml) was added. After stirring for 24h the yellow solid was collected to give compound (209b), (83%), as tiny, yellow needles, m.p. 277° (from acetic acid-water).

Found: C, 63.8%; H, 4.0%; N, 13.1%.

$C_{17}H_{13}N_3O_4$ requires: C, 63.2%; H, 4.1%; N, 13.0%.

2.6. Attempted Reaction of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxide (199a) with Nucleophiles.

A suspension of 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.001 mol) in ethanol (6.0 ml) was heated under reflux with (a) aniline (0.001 mol), and (b) ethyl cyanoacetate (0.001 mol), for 2h. The yellow solid obtained by hot filtration was combined with the precipitate which separated on cooling. A further, small amount of material was obtained by evaporating the mother-liquors under reduced pressure and triturating the residual gum with ether-light petroleum. The combined fractions afforded the starting N-oxide (88-92% recovery).

2.7. Reaction of the 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199) and (209a) with Sodium Ethoxide.

The 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199) or (209a) (0.02 mol) was heated under reflux for 2h with a solution of sodium (0.03g atom) in dry ethanol (100 ml). Evaporation of the reaction mixture under reduced pressure gave a yellow solid which was washed with water and filtered to afford [except in (iii) - see below] unreacted starting material. Acidification of the filtrate with 2N aqueous hydrochloric acid gave a pale yellow solid which was collected and dried to afford the corresponding 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202) or (210a), ^1H n.m.r. spectra, Table 4.

(i) 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) was obtained as pale yellow prisms, (67%; 74% based on recovered starting material), m.p. 196° (from benzene-light petroleum), ν_{max} . 2800-2600 $\text{br}(\text{OH})$, and 1610 cm^{-1} .

Found: C, 65.9%; H, 4.0%; N, 11.1%.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$ requires: C, 66.1%; H, 4.0%; N, 11.0%.

Earlier attempts had been made to obtain this compound as follows:-

(a) A solution of 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.001 mol) in glacial acetic acid (5.0 ml) was treated with 20% (w/v) aqueous sulphuric acid and heated under reflux for 3h. The reaction mixture was concentrated and filtered, and the residue was well washed with water, to afford the starting di-N-oxide (88% recovery).

(b) 3-Cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.01 mol) was heated under reflux in 10% aqueous sodium hydroxide

(80.0 ml) for 1h. Hot filtration and acidification of the filtrate to pH 7 with 2N aqueous hydrochloric acid afforded 3-carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201a) (21%), identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained as described below. Further acidification to pH 1 with 2N aqueous hydrochloric acid (acidification with dilute sulphuric acid complicated the work-up because of the formation of a stable salt) afforded 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) (72%), identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained as described above.

(ii) 4-Hydroxy-6-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202b) was obtained as yellow needles (76%; quantitative yield based on recovered starting material), m.p. 218° (from benzene-light petroleum), ν_{\max} . 2700-2600 br (OH), and 1605 (CO) cm^{-1} .

Found: C, 67.2%; H, 4.5%; N, 10.3%.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 67.2%; H, 4.5%; N, 10.4%.

(iii) 4-Hydroxy-6-methoxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202c) was obtained as pale yellow needles (76%), m.p. 243° (from benzene-light petroleum), ν_{\max} . 2750-2600 br (OH), 1670 (CO) and 1605 cm^{-1} .

Found: C, 63.6%; H, 4.1%; N, 9.5%.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4$ requires: C, 63.4%; H, 4.3%; N, 9.9%.

This product was accompanied by an initially insoluble residue (see above) which proved to be 3-carbamoyl-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (201c) (15%), identical

(m.p., mixed m.p. and i.r. spectrum) with an authentic sample prepared as described below.

(iv) 6-Bromo-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202d) was obtained as yellow platelets, (80%; 99% based on recovered starting material), m.p. 231° (from benzene), ν_{\max} . 2700-2400 br (OH), 1650 (CO) and 1600 cm^{-1} .

Found: C, 50.8%; H, 2.8%; N, 9.0%.

$C_{14}H_9BrN_2O_3$ requires: C, 50.5%; H, 2.7%; N, 8.4%.

(v) 6-Chloro-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202e) was obtained as pale yellow needles, (75%), m.p. 228° (from benzene), ν_{\max} . 2700-2600 br (OH), and 1610-1600 br (CO) cm^{-1} .

Found: C, 58.3%; H, 2.8%; N, 9.8%.

$C_{14}H_9ClN_2O_3$ requires: C, 58.2%; H, 3.1%; N, 9.7%.

(vi) 6,7-Dimethyl-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (210a) was obtained as yellow needles, (70%; 91% based on recovered starting material), m.p. 225° (from benzene-ethanol), ν_{\max} . 2700-2650 br (w)(OH), and 1605 (CO) cm^{-1} .

Found: C, 67.5%; H, 4.7%; N, 9.5%.

$C_{16}H_{14}N_2O_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

2.8. Acid Hydrolysis of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199).

The 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199) (0.005 mol) was treated with concentrated sulphuric acid (5.0 ml) and water (0.2 ml) giving a red solution. The reaction mixture was heated on a water bath at 60° for 5h

and then poured onto ice (7.5g). The pale yellow solid thus obtained was filtered off, washed well with water and crystallised from acetic acid-water to yield the 3-carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201), ν_{\max} . 3375 and 3175 (NH), and 1680 (CO) cm^{-1} .

(i) 3-Carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201a) was obtained as pale yellow needles, (82%), m.p. 270° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.22 (2H, m, Ar-H), 1.80 (2H, m, Ar-H), and 2.34 (5H, s, Ar-H).

Found: C, 64.2%; H, 3.9%; N, 15.1%; M^+ , 281.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$ requires: C, 64.1%; H, 3.9%; N, 14.9%; M, 281.

(ii) 3-Carbamoyl-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (201c) was obtained as pale yellow needles, (81%), m.p. 259° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.33 (1H, d, J 9.5 Hz, H-8), 1.96 (1H, d, J 2.5 Hz, H-5), 2.17 (1H, dd, J_m 2.5 Hz, J_o 9.5 Hz, H-7), 2.37 (5H, s, Ar-H), and 5.85 (3H, s, OCH_3).

Found: C, 62.1%; H, 4.3%; N, 13.9%.

$\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$ requires: C, 61.7%; H, 4.2%; N, 13.5%.

2.9. Preparation of 2-Nitro- α -phenylacetanilides (214) and (219).

The 2-nitro- α -phenylacetanilides (214) and (219) were prepared according to the method of Tennant.¹⁴⁸

The α -nitroaniline derivative (195) or (207) (0.1 mol) was heated with phenylacetyl chloride (13.4 ml, 0.1 mol) in dry benzene (50.0 ml) on a boiling water bath for 2h. Removal of the solvent under reduced pressure gave a gum which crystallised on rubbing to give the corresponding 2-nitro- α -phenylacetanilide (214) or (219).

(i) 2-Nitro- α -phenylacetanilide (214a) (71%), had m.p. 79° (lit., $^{148} 84^{\circ}$), ν_{\max} . 3325 (NH), 1690 (CO) and 1580 cm^{-1} .

(ii) 4-Methyl-2-nitro- α -phenylacetanilide (214b) was obtained as pale yellow needles in quantitative yield, m.p. 94° (from benzene-light petroleum), ν_{\max} . 3300 and 3250 (NH), 1700 and 1670 (CO), 1580, and 1520 and 1340 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.65 (1H, d, J 8.75 Hz, H-6), 1.97 (1H, d, J 1.5 Hz, H-3), 2.43 (1H, dd, J_o 8.75 Hz, J_m 1.5 Hz, H-5), 2.58 (5H, m, Ar-H), 5.98 (2H, s, CH_2), and 7.56 (3H, s, CH_3).

Found: C, 66.9%; H, 5.1%; N, 10.4%.

$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 66.7%; H, 5.2%; N, 10.4%.

(iii) 4-Methoxy-2-nitro- α -phenylacetanilide (214c) (98%), had m.p. 84° (lit., $^{149} 84^{\circ}$), ν_{\max} . 3300 (NH), 1660 (CO), 1580, and 1520 and 1350 (NO_2) cm^{-1} .

(iv) 4-Bromo-2-nitro- α -phenylacetanilide (214d) was obtained as yellow needles in quantitative yield, m.p. 124° (from benzene-light petroleum), ν_{\max} . 3350 (NH), 1685 (CO), 1580, and 1500 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.52 (1H, d, J 9.0 Hz, H-6), 1.70 (1H, d, J 2.25 Hz, H-3), 2.18 (1H, dd, J_o 9.0 Hz, J_m 2.25 Hz, H-5), 2.60 (5H, m, Ar-H), and 6.00 (2H, s, CH_2).

Found: C, 50.6%; H, 3.3%; N, 8.6%.

$\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}_3$ requires: C, 50.1%; H, 3.3%; N, 8.4%.

(v) 4-Chloro-2-nitro- α -phenylacetanilide (214e) (70%), had m.p. 103° (lit., $^{149} 110^{\circ}$), ν_{\max} . 3300 (NH), 1680 (CO), 1580, and 1520 and 1360 (NO_2) cm^{-1} .

(vi) 4,5-Dimethyl-2-nitro- α -phenylacetanilide (219a) was obtained as pale yellow needles, (87%), m.p. 170° (from benzene), ν_{\max} . 3300 (NH), 1675 (CO), 1580, and 1540 and 1360 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.75 (1H, s, H-3), 2.03 (1H, s, H-6), 2.57 (5H, s, Ar-H), 6.00 (2H, s, CH_2), 7.61 (3H, s, CH_3), and 7.68 (3H, s, CH_3).

Found: C, 68.0%; H, 5.4%; N, 9.7%.

$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$ requires: C, 67.6%; H, 5.7%; N, 9.9%.

(vii) 4,5-Dimethoxy-2-nitro- α -phenylacetanilide (219b) was obtained as yellow needles, (66%), m.p. 151° (from benzene-light petroleum), ν_{\max} . 3275 (NH), 1675 (CO), 1585, and 1520 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.59 (1H, s, H-3), 2.20 (1H, s, H-6), 2.58 (5H, m, Ar-H), 5.94 (3H, s, OCH_3), 5.98 (2H, s, CH_2), and 6.01 (3H, s, OCH_3).

Found: C, 60.6%; H, 5.0%; N, 8.6%.

$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$ requires: C, 60.8%, H, 5.1%; N, 8.9%.

(viii) 2,4-Dinitro- α -phenylacetanilide (214f) was obtained as pale yellow needles (70%; 98% based on recovered starting material, obtained by hot filtration of the reaction mixture), m.p. 112° (from benzene-light petroleum), ν_{\max} . 3325 (NH), 1710 (CO), 1600, and 1520 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.98 (1H, d, J 9.0 Hz, H-3), 1.03 (1H, d, J 2.5 Hz, H-6), 1.50 (1H, dd, J_m 2.5 Hz, J_o 9.0 Hz, H-5), 2.58 (3H, m, Ar-H), 2.76 (2H, m, Ar-H) and 5.97 (2H, s, CH_2).

Found: C, 55.0%; H, 3.7%; N, 13.7%.

$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_5$ requires: C, 55.8%; H, 3.7%; N, 14.0%.

2.10. Preparation of 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides (215) and (220a).

A series of 2-phenylquinoxalin-3(4H)-one 1-N-oxides (215) and (220a) was prepared according to the method of Ahmad.¹⁴⁹

The 2-nitro- α -phenylacetanilide derivative (214) or (219) (0.02 mol) was dissolved in a mixture of pyridine (25.0 ml) and 20% aqueous potassium hydroxide (25.0 ml) and the mixture was heated on a boiling water bath for 1h with vigorous stirring. The reaction mixture was diluted with water and the precipitated o-nitroaniline derivative (formed by competing hydrolysis of the 2-nitro- α -phenylacetanilide) was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and the yellow solid was collected and washed with water to afford the corresponding 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215) or (220a), ¹H n.m.r. spectra, Table 3.

(i) 2-Phenylquinoxalin-3(4H)-one 1-N-oxide (215a) (60%), had m.p. 282-6° (lit.,^{148,149} 285°; 307°), ν_{\max} . 1650 (CO) and 1620 cm^{-1} .

(ii) 7-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215b) was obtained as pale yellow needles, (34%), m.p. 296° (from acetic acid-water), ν_{\max} . 3150 (NH) and 1640 (CO) cm^{-1} .

Found: C, 71.3%; H, 4.6%; N, 11.0%.

C₁₅H₁₂N₂O₂ requires: C, 71.4%; H, 4.8%; N, 11.1%.

4-Methyl-2-nitroaniline (195b) (28%) was obtained as by-product, identical (m.p. and i.r. spectrum) with an authentic sample.

(iii) 7-Methoxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215c) (66%), had m.p. 287° (lit.,¹⁴⁹ $297-300^{\circ}$), ν_{\max} . 1650 (CO) and 1600 cm^{-1} .

(iv) 7-Bromo-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215d) was obtained as yellow platelets, (56%), m.p. 298° (from acetic acid-water), ν_{\max} . 1660 (CO) and 1620 cm^{-1} .

Found: C, 53.1%; H, 2.8%; N, 8.8%.

$\text{C}_{14}\text{H}_9\text{BrN}_2\text{O}_2$ requires: C, 53.0%; H, 2.8%; N, 8.8%.

(v) 7-Chloro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215e) (67%), had m.p. 286° [lit.,¹⁴⁹ 313° (decomp.)], ν_{\max} . 1650 (CO) and 1620 cm^{-1} .

(vi) 6,7-Dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (220a) was obtained as yellow needles, (43%), m.p. 286° (from acetic acid-water), ν_{\max} . 1660 (CO) and 1630 cm^{-1} .

Found: C, 72.2%; H, 4.9%; N, 10.0%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

4,5-Dimethyl-2-nitroaniline (207a) (48%), was obtained as by-product, m.p. 139° (lit.,¹⁹⁰ 140°).

(vii) Attempted cyclisation of 4,5-dimethoxy-2-nitro- α -phenyl-acetanilide (219b) afforded 4,5-Dimethoxy-2-nitroaniline (207b) (76%) as the sole product, m.p. 170° (lit.,¹⁹² 170°).

(viii) 7-Nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) was obtained as buff platelets, (55%), m.p. 276° (from glacial acetic acid), ν_{\max} . 1680 (CO) and 1620 cm^{-1} .

Found: C, 59.3%; H, 3.1%; N, 14.8%.

$\text{C}_{14}\text{H}_9\text{N}_3\text{O}_4$ requires: C, 59.4%; H, 3.2%; N, 14.8%.

2,4-Dinitroaniline (19%) was obtained as by-product, identical with an authentic sample.

2.11. Preparation of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (216) and (220b).

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215) or (220a) (1.0g) was dissolved in 10% aqueous sodium hydroxide (10.0 ml) and dimethyl sulphate (2.5 ml) was added dropwise with vigorous shaking, always keeping the solution alkaline. The reaction mixture was heated on a boiling water bath for 15 min and the yellow solid which separated on cooling was collected, dried and crystallised to afford the corresponding N-methyl derivative (216) or (220b), ^1H n.m.r. spectra, Table 3.

(i) 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) was obtained in quantitative yield, identical (m.p. and i.r. spectrum) with an authentic sample.¹⁴⁸

(ii) 4,7-Dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216b) was obtained as pale yellow needles, (77%), m.p. 238° (from acetic acid-water), ν_{max} . 1630 (CO) and 1590 cm^{-1} .

Found: C, 72.1%; H, 5.4%; N, 10.4%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

(iii) 7-Methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216c) was obtained as orange cubes in quantitative yield, m.p. 279° (from acetic acid-ethanol), ν_{max} . 1630 cm^{-1} .

Found: C, 68.0%; H, 4.9%; N, 9.4%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

(iv) 7-Bromo-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216d) was obtained as pale yellow needles, (77%), m.p. 219° (from acetic acid-water), ν_{\max} . 1635 (CO) and 1610 cm^{-1} .

Found: C, 54.3%; H, 3.2%; N, 8.5%.

$C_{15}H_{11}BrN_2O_2$ requires: C, 54.4%; H, 3.3%; N, 8.5%.

(v) 7-Chloro-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216e) was obtained as pale yellow needles, (90%), m.p. 190° (from acetic acid-water), ν_{\max} . 1640 (CO) and 1580 cm^{-1} .

Found: C, 62.4%; H, 5.7%; N, 9.8%.

$C_{15}H_{11}ClN_2O_2$ requires: C, 62.8%; H, 5.8%; N, 10.0%.

(vi) 2-Phenyl-4,6,7-trimethylquinoxalin-3(4H)-one 1-N-oxide (220b) was obtained as yellow needles, (92%), m.p. 200° (from acetic acid-water), ν_{\max} . 1630 (CO) and 1620 cm^{-1} .

Found: C, 73.4%; H, 5.7%; N, 9.8%.

$C_{17}H_{16}N_2O_2$ requires: C, 72.8%; H, 5.8%; N, 10.0%.

(vii) 4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216f).

The above method only succeeded in forming the sodium salt of the starting material (215f), even when the reaction mixture was shaken for 12h.

7-Nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) (0.5 g) was heated under reflux in anhydrous acetone (50.0 ml) with anhydrous potassium carbonate (1.5 g). Dimethyl sulphate (1.0 ml) was added dropwise and heating was continued for 4h. The reaction mixture was evaporated under reduced pressure and the residue was treated with water giving a yellow gummy solid which was extracted into chloroform. Evaporation of

the extract gave the compound (216f) as yellow needles, (79%), m.p. 208° (from ethanol-acetic acid), ν_{\max} . 1660 (CO), 1610, and 1535 and 1350 (NO_2) cm^{-1} .

Found: C, 60.7%; H, 3.6%; N, 14.2%.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_4$ requires: C, 60.6%; H, 3.7%; N, 14.1%.

2.12. Preparation of 2-Phenylquinoxalin-3(4H)-ones (204), (211), (217) and (218).

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (202), (210a), (215), (216) or (220) (0.5 g) was heated under reflux with twice its weight of sodium dithionite (added in two portions, the second portion after 1h) in 70% v/v aqueous ethanol (10.0 - 50.0 ml) for 2h. Filtration and concentration of the reaction mixture yielded a solid which was washed with water, dried and crystallised from ethanol or acetic acid to give the corresponding 2-phenylquinoxalin-3(4H)-one derivative (204), (211a) or (217), ν_{\max} . 1660 (CO) cm^{-1} , or (211b) or (218), ν_{\max} . 1640 (CO) cm^{-1} , ^1H n.m.r. spectra, Table 3.

(i) 2-Phenylquinoxalin-3(4H)-one (204a).

(a) Reduction of compound (215a) afforded compound (204a), (81%), m.p. 253° (lit.,¹⁴⁹ 260°).

(b) Reduction of compound (202a) afforded compound (204a), (69%), m.p. 256° , identical (mixed m.p. and i.r. spectrum) with an authentic sample.¹⁴⁹

(ii) 4-Methyl-2-phenylquinoxalin-3(4H)-one (218a) was obtained by reducing compound (216a), (90%), m.p. 135° (lit.,¹⁴⁹ 138°).

(iii) 6-Methyl-2-phenylquinoxalin-3(4H)-one (204b) was obtained by reducing compound (202b), as pale yellow needles, (83%),

m.p. 237° (from ethanol-water).

Found: C, 76.5%; H, 5.0%; N, 11.9%.

C₁₅H₁₂N₂O requires: C, 76.3%; H, 5.1%; N, 11.9%.

(iv) 7-Methyl-2-phenylquinoxalin-3(4H)-one (217b) was obtained by reducing compound (215b), as pale yellow needles, in quantitative yield, m.p. 248° (from ethanol).

Found: C, 76.2%; H, 5.1%; N, 11.7%.

C₁₅H₁₂N₂O requires: C, 76.3%; H, 5.1%; N, 11.9%.

(v) 4,7-Dimethyl-2-phenylquinoxalin-3(4H)-one (218b) was obtained by reducing compound (216b), as pale yellow needles, (85%), m.p. 144° (from ethanol).

Found: C, 77.4%; H, 5.5%; N, 10.6%.

C₁₆H₁₄N₂O requires: C, 76.8%; H, 5.6%; N, 11.2%.

(vi) 6-Methoxy-2-phenylquinoxalin-3(4H)-one (204c) was obtained by reducing compound (202c), as cream needles, in quantitative yield, m.p. 239° (from acetic acid-water).

Found: C, 70.8%; H, 4.8%; N, 11.4%.

C₁₅H₁₂N₂O₂ requires: C, 71.4%; H, 4.8%; N, 11.1%.

(vii) 7-Methoxy-2-phenylquinoxalin-3(4H)-one (217c) was obtained by reducing compound (215c), as small yellow needles, in quantitative yield, m.p. 249° (lit., ¹⁴⁹ 235°) (from acetic acid-water).

Found: C, 71.3%; H, 4.5%; N, 10.7%.

Calc. for C₁₅H₁₂N₂O₂: C, 71.4%; H, 4.8%; N, 11.1%.

(viii) 7-Methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (218c) was obtained by reducing compound (216c), as a yellow solid,

(82%), m.p. 165.5° (from acetic acid-ethanol).

Found: C, 72.3%; H, 5.4%; N, 10.7%.

$C_{16}H_{14}N_2O_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

(ix) 6-Bromo-2-phenylquinoxalin-3(4H)-one (204d) was obtained by reducing compound (202d), as yellow needles, (94%), m.p. 287° (from acetic acid-ethanol).

Found: C, 55.3%; H, 3.1%; N, 9.0%.

$C_{14}H_9BrN_2O$ requires: C, 55.8%; H, 3.0%; N, 9.3%.

(x) 7-Bromo-2-phenylquinoxalin-3(4H)-one (217d) was obtained by reducing compound (215d), as pale yellow needles, (74%), m.p. 298° (from acetic acid-water).

Found: C, 55.7%; H, 2.9%; N, 9.1%.

$C_{14}H_9BrN_2O$ requires: C, 55.8%; H, 3.0%; N, 9.3%.

(xi) 7-Bromo-4-methyl-2-phenylquinoxalin-3(4H)-one (218d) was obtained by reducing compound (216d), as pale yellow needles, (76%), m.p. 173.5° (from acetic acid-ethanol).

Found: C, 57.5%; H, 3.5%; N, 9.2%.

$C_{15}H_{11}BrN_2O$ requires: C, 57.1%; H, 3.5%; N, 8.9%.

(xii) 6-Chloro-2-phenylquinoxalin-3(4H)-one (204e) was obtained by reducing compound (202e), as pale yellow needles, (93%), m.p. 265.5° (from acetic acid-water) (lit.,¹³⁸ 275°)

Found: C, 65.8%; H, 3.4%; N, 10.9%.

Calc. for $C_{14}H_9ClN_2O$: C, 65.5%; H, 3.5%; N, 10.9%.

(xiii) 7-Chloro-2-phenylquinoxalin-3(4H)-one (217e) was obtained by reducing compound (215e), in quantitative yield, m.p. 258° (lit.,¹⁴⁹ 263°).

but failed to yield acetyl derivatives.

Ahmad¹⁷⁰ has reported that heating 2-cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) with aniline gives a product formulated as (271a). The m.p.s of Ahmad's compound (248°) and that of the product derived from the reaction of the N-oxide (270a) with phenyl isocyanate, (252°), are very similar. Consequently the reaction of the cyano-N-oxide (193c) with aniline was carried out in the hope of establishing unambiguously the structure of the product obtained by cyclo-addition. However, when the cyano-N-oxide (193c) was heated under reflux with excess aniline in dry xylene, the N-oxide (193c) was recovered unchanged. Elevation of the reaction temperature by heating the two reagents in dimethylformamide resulted in the formation of an intractable tar. Similar attempts to convert the N-methyl-N-oxide (193d) into the compound (271c) were also unsuccessful. Thus, heating the N-oxide (193d) in aniline also gave an intractable tar. Alternatively, when the N-oxide (193d) and aniline were heated in dry xylene, an amorphous brown solid was obtained which was not identical with the product derived from the N-oxide (270b) and phenyl isocyanate and did not possess spectral (i.r.) properties consistent with the expected structure (271c).

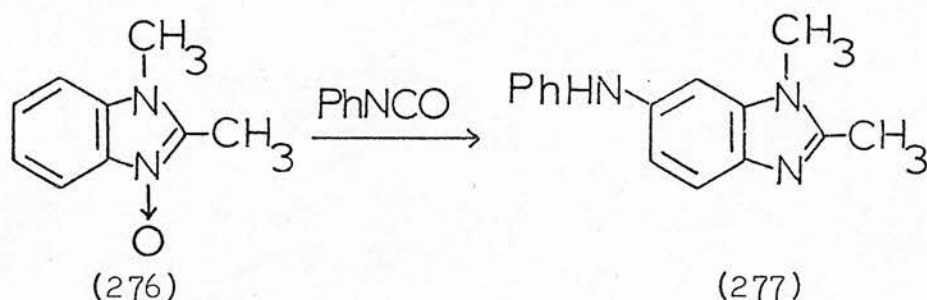
It had previously been shown that the 2-chloro-group in 2-chloro-4-methylquinoxalin-3(4H)-one (273) is susceptible to nucleophilic displacement by methoxide ion¹⁷¹ and by N-methylaniline.¹⁷² Application of this type of nucleophilic displacement using aniline should therefore yield

the desired N-phenylamino-derivative (271c). When the readily available¹⁷¹ 2-chloro-4-methylquinoxalin-3(4H)-one (273) was heated with two equivalents of aniline, in dry xylene, a solid separated out, which was water soluble, and was shown by its i.r. spectrum to be aniline hydrochloride. Work-up of the reaction mixture afforded a crystalline solid in high yield, which was identical with the product of the reaction of phenyl isocyanate with the N-oxide (270b), thus confirming its structure as (271c). The product obtained from the N-oxide (270a) is assigned the N-phenylamino-structure (271a) by analogy.

To see if the dipolar reactivity of the N-oxides (270a-b) could be extended to other isocyanates the reactions of these compounds with p-chlorophenyl isocyanate and methyl isocyanate were next studied. The N-oxide (270b), on heating with p-chlorophenyl isocyanate in dry xylene, afforded a chlorine-containing compound resembling the N-phenylamino-derivative (271c) in its properties. Its structure was established as (271d) by showing it to be identical with the product obtained by heating 2-chloro-4-methylquinoxalin-3(4H)-one (273) with p-chloroaniline. In contrast, the N-oxide (270a) was recovered unchanged when it was heated with p-chlorophenyl isocyanate in dimethylformamide. The only product isolated in this reaction was identified as di-(p-chlorophenyl)urea. None of the expected product (271b) could be detected in the reaction mixture. The use of excess p-chlorophenyl isocyanate in this reaction gave the same

result. Both N-oxides (270a-b) were recovered unchanged on attempted reaction with methyl isocyanate.

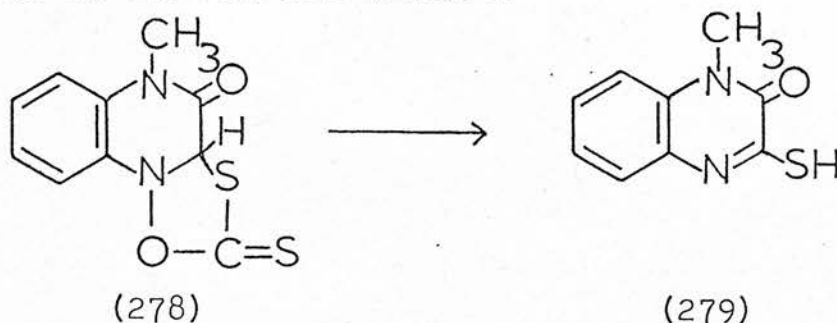
Although no intermediate isoxazolidines were isolated in the reactions of the N-oxides (270a-b) with phenyl- and *p*-chlorophenyl isocyanate, compounds of this type are probable intermediates in the formation of the amines (271). It is worth noting however, that one instance is known in which phenyl isocyanate appears to react with an N-oxide in a different manner. 1,2-Dimethylbenzimidazole 3-N-oxide (276) in which the 2-position is blocked affords the N-phenylamino-derivative (277), presumably by a process involving nucleophilic substitution.¹⁴⁴



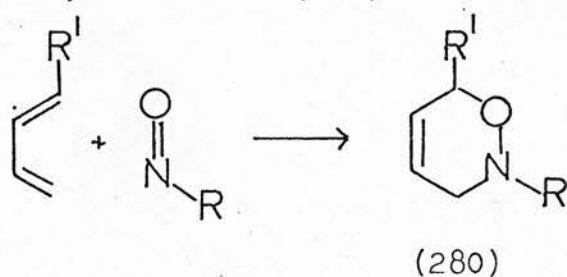
It can be seen from the present results that 1,3-dipolar cycloaddition is a useful route to 2-arylamino-quinoxalin-3(4H)-ones (271). Nucleophilic displacement of the 2-chloro-group in 2-chloro-4-methylquinoxalin-3(4H)-one (273) by arylamines appears to be the only alternative method. The reactivity of the 2-chloro-compound (273) towards nucleophilic displacement by amines was shown to be quite general. Heating with benzylamine and diethylamine afforded the corresponding amino-derivatives (274) and (275). The compound (275) was isolated as an oil and was characterised

as its picrate. Attempted displacement of the 2-chloro-group in compound (273) with ethyl carbamate was, however, unsuccessful.

Carbon disulphide has been widely used as a dipolarophile in 1,3-dipolar cycloaddition reactions but failed to react with the N-oxide (270b). None of the thiol (279), derived by loss of COS from the intermediate adduct (278) could be detected in the reaction mixture.

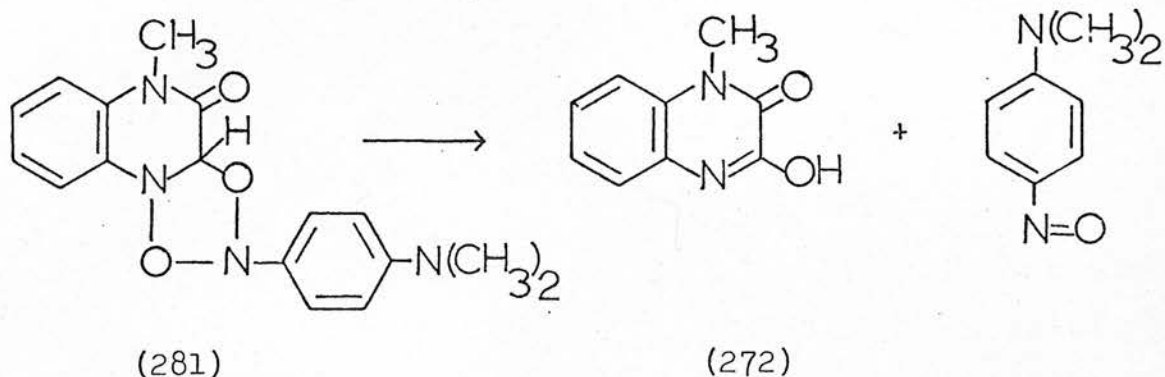


Kresze¹⁷³ has shown that 2 + 4 cycloaddition is a good method for the preparation of heterocyclic compounds when the dienophile contains heteroatoms. Aromatic nitroso compounds react readily with dienes in this way to afford 3,6-dihydro-1,2-oxazines (280).

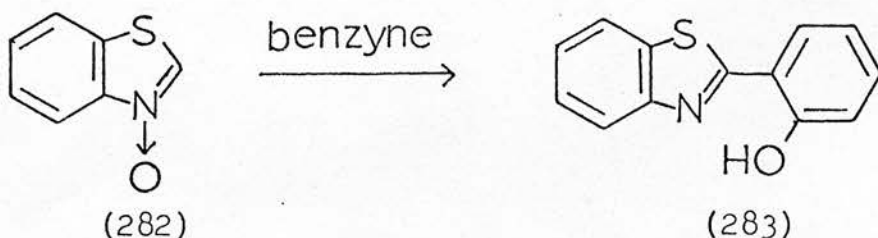


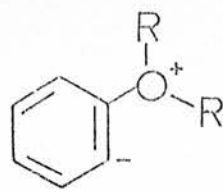
It was therefore of interest to see if this reactivity could be extended to 1,3-dipolar cycloadditions. Nitroso compounds do not appear to have been studied in this context.

p-Nitroso-N,N-dimethylaniline could in theory react with the N-oxide (270b) to yield the adduct (281). Alternatively, ring-opening of the adduct (281), as shown, might be expected to yield the 2-hydroxy-derivative (272) with re-generation of the nitroso compound. However, an attempt to condense the N-oxide (270b) with p-nitroso-N,N-dimethylaniline was unsuccessful.

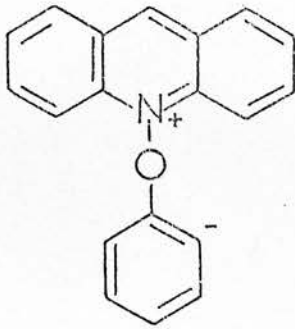


Many examples are known of 1,3-dipoles reacting with dipolarophiles containing a triple bond such as methyl propiolate. The inclusion of benzyne in these studies has opened up preparative routes to many benzo-heterocycles. Ethers and cyclic ethers are known to react with benzyne to form betaines of the type (284). The oxygen atom in heterocyclic N-oxides is even more basic and should therefore react with benzyne even more readily. Recently, Kano¹⁷⁴ has shown that benzothiazole 3-N-oxide (282) reacts with benzyne to form the hydroxyphenyl derivative (283).

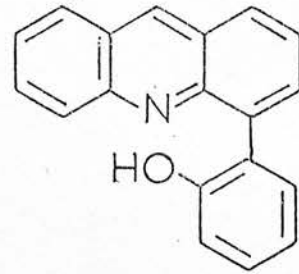




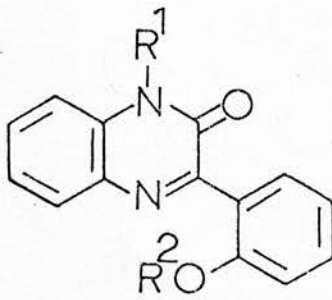
(284)



(285)

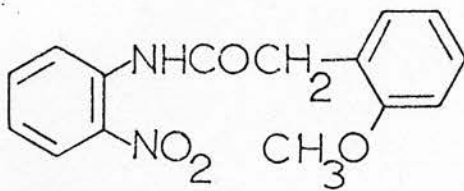


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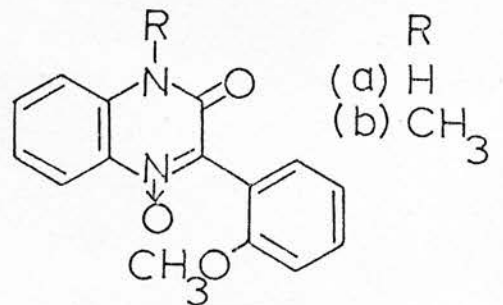


(287)

	R ¹	R ²
(a)	H	H
(b)	CH ₃	H
(c)	H	CH ₃
(d)	CH ₃	CH ₃



(288)

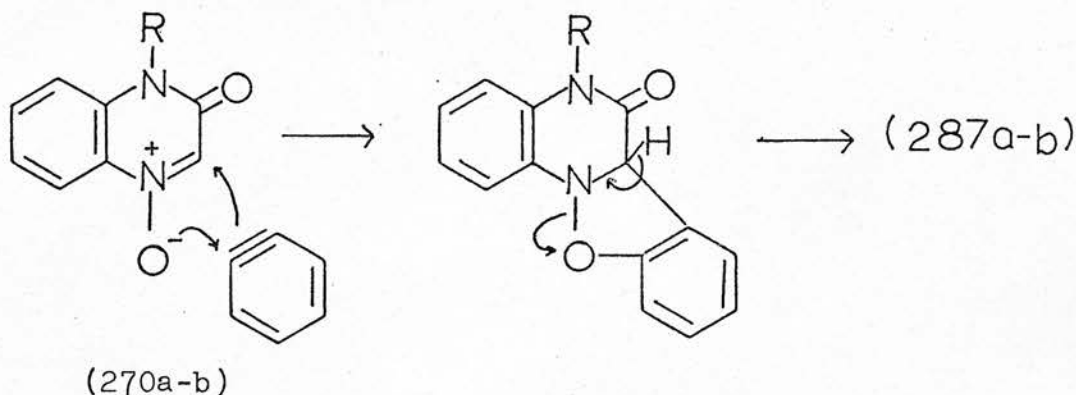


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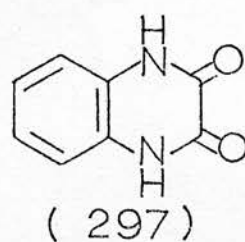
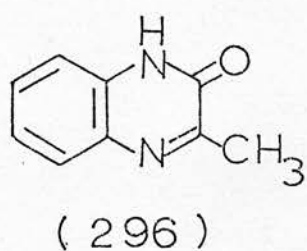
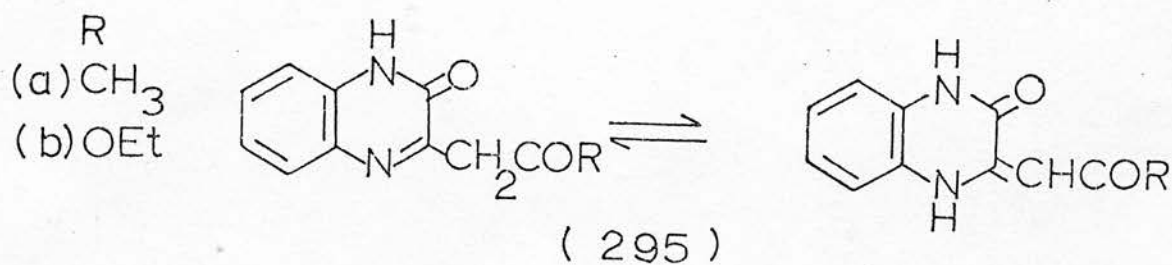
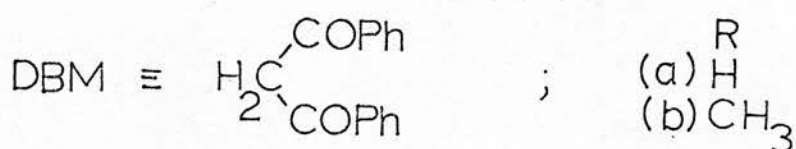
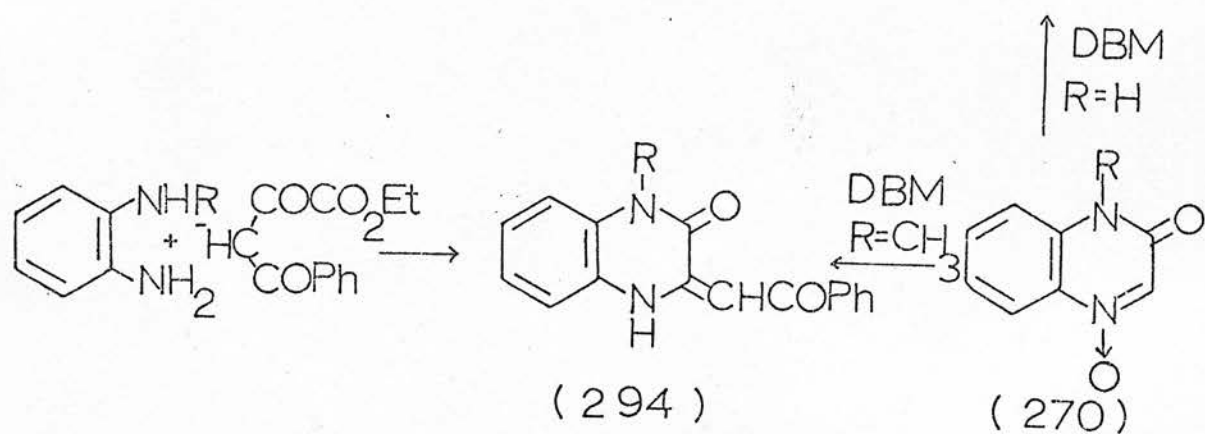
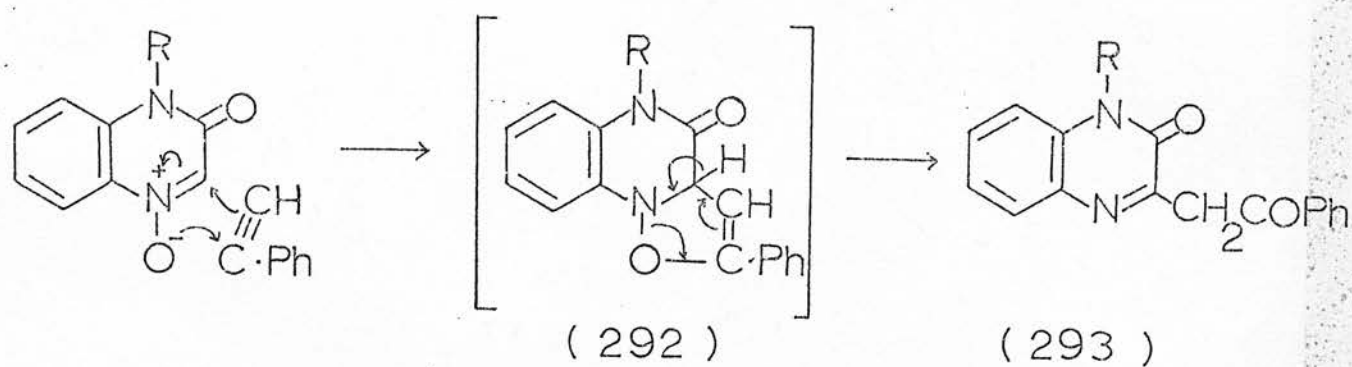
	R
(a)	H
(b)	CH ₃

Likewise, acridine 10-N-oxide reacts with benzyne to give the compound (286) in 25% yield.¹⁷⁵ The first step in this reaction may well be generation of the betaine (285) but subsequent steps are not yet clear.

When the N-oxides (270a-b) were heated in the presence of benzyne, generated by the aprotic method,¹⁷⁶ quantitative or near quantitative yields of products were obtained. These products were soluble in alkali and gave a deep red colour with iron (III) chloride in ethanol. This evidence suggested the presence of a phenolic group and hence the structures (287a-b) for the products.



The product derived from the N-oxide (270a) was methylated to afford a compound identical with that obtained from the N-oxide (270b) and benzyne. Further methylation afforded a dimethyl derivative. This dimethyl derivative is assigned the structure (287d) on the basis of its unambiguous synthesis. Condensation of 2-methoxyphenylacetyl chloride with o-nitroaniline yielded the anilide (288). Cyclisation¹⁴⁹ under basic conditions afforded the 1-N-oxide (289a) in poor yield. The major products of this reaction were o-nitroaniline and 2-methoxyphenylacetic acid, formed by hydrolysis of the anilide (288). Hydrolysis rather than cyclisation of the



anilide (288) is presumably due to deactivation of the methylene group in the side-chain by the o-methoxyphenyl substituent.

Dithionite reduction of the 1-N-oxide (289a) afforded the quinoxalin-3(4H)-one (287c) which was isomeric with the product derived from the N-oxide (270b) and benzyne, but had different properties. Methylation of the N-oxide (289a), followed by dithionite reduction afforded the compound (287d) which proved to be identical with the product of complete methylation of both compounds obtained by reaction of the N-oxides (270a-b) with benzyne.

It is well known that 1,3-dipolar cycloaddition reactions occur with alkenes and alkynes, particularly those substituted with electron-withdrawing groups (e.g. $C \equiv N$, CO_2R). The reactivity of aryl alkynes does not appear to have been studied in this respect. Phenylacetylene might be expected to react as a dipolarophile with the N-oxides (270a-b). Potentially, this reaction could afford two different products depending on the mode of addition of the acetylene derivative. The ketones (293) would arise from the adducts (292) whereas if addition occurs in the opposite direction to give the adducts (290), the aldehydes (291) would be the final products. The N-oxides (270a-b) were found to react readily with phenylacetylene (see later). However, unambiguous synthesis of the ketones (293) has shown them to be different from the products obtained from the N-oxides (270a-b) and phenylacetylene.

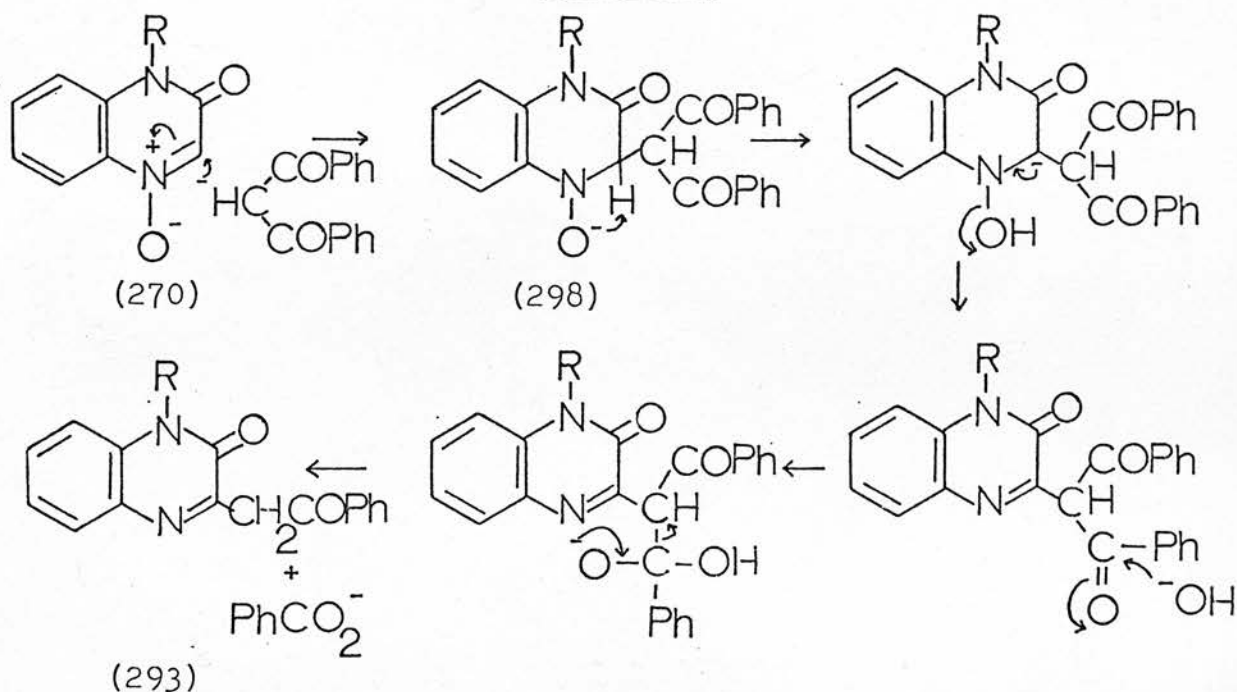
Condensation of o-phenylenediamine with ethyl benzoyl-

pyruvate afforded a yellow solid which analysed correctly for the ketone (293a). In support of this structure alkaline hydrolysis with 20% aqueous potassium hydroxide afforded 2-methylquinoxalin-3(4H)-one (296) and benzoic acid. Also, chromic acid oxidation yielded quinoxalin-2,3(1H,4H)-dione (297) and benzoic acid. However, the ^1H n.m.r. spectrum run in deuterated dimethylsulphoxide or in trifluoroacetic acid contained no absorption attributable to a methylene group. Other investigators^{177,178} have shown that quinoxalin-3(4H)-ones of the type (295) can exist in the two possible tautomeric forms shown, the predominant form depending on the solvent. Examination of the ^1H n.m.r. spectrum of the compound (295b) in deuterated dimethylsulphoxide indicated that in this solvent the predominant tautomer was that with the exocyclic double bond. On the other hand, in trifluoroacetic acid the alternative tautomer predominates. For the methyl ketone (295a) the predominant tautomer in both solvents is the form with the exocyclic double bond. Comparison of these spectra with that of the condensation product above showed that the yellow ketone existed solely in the tautomeric form (294a). Condensation of N-methyl-o-phenylenediamine with ethyl benzoylpyruvate afforded the corresponding N-methyl-derivative (294b) whose ^1H n.m.r. spectrum also possessed a signal attributable to an olefinic proton. The compound (294b) was also obtained by methylation of the quinoxalone (294a).

The quinoxalin-3(4H)-one 1-N-oxides (270a-b) are

known¹⁷⁹ to react with methylene compounds, substitution occurring at the 2-position. By analogy, dibenzoylmethane might be expected to react with the N-oxides (270a-b) forming initial adducts (298) convertible into the ketones (293) as shown (Scheme 11).

Scheme 11



The N-oxide (270a) condensed readily with dibenzoylmethane in the presence of piperidine to afford a yellow solid, identical with the yellow ketone (294a), but amounting to only 2% of the product. The main product was a white solid, isomeric with the yellow ketone (294a). In reactions similar to those of the latter, the white solid was converted by treatment with 20% aqueous potassium hydroxide and chromic acid into the quinoxalones (296) and (297) respectively. On the basis of these transformations and the presence of signals attributable to a methylene group in the ^1H n.m.r.

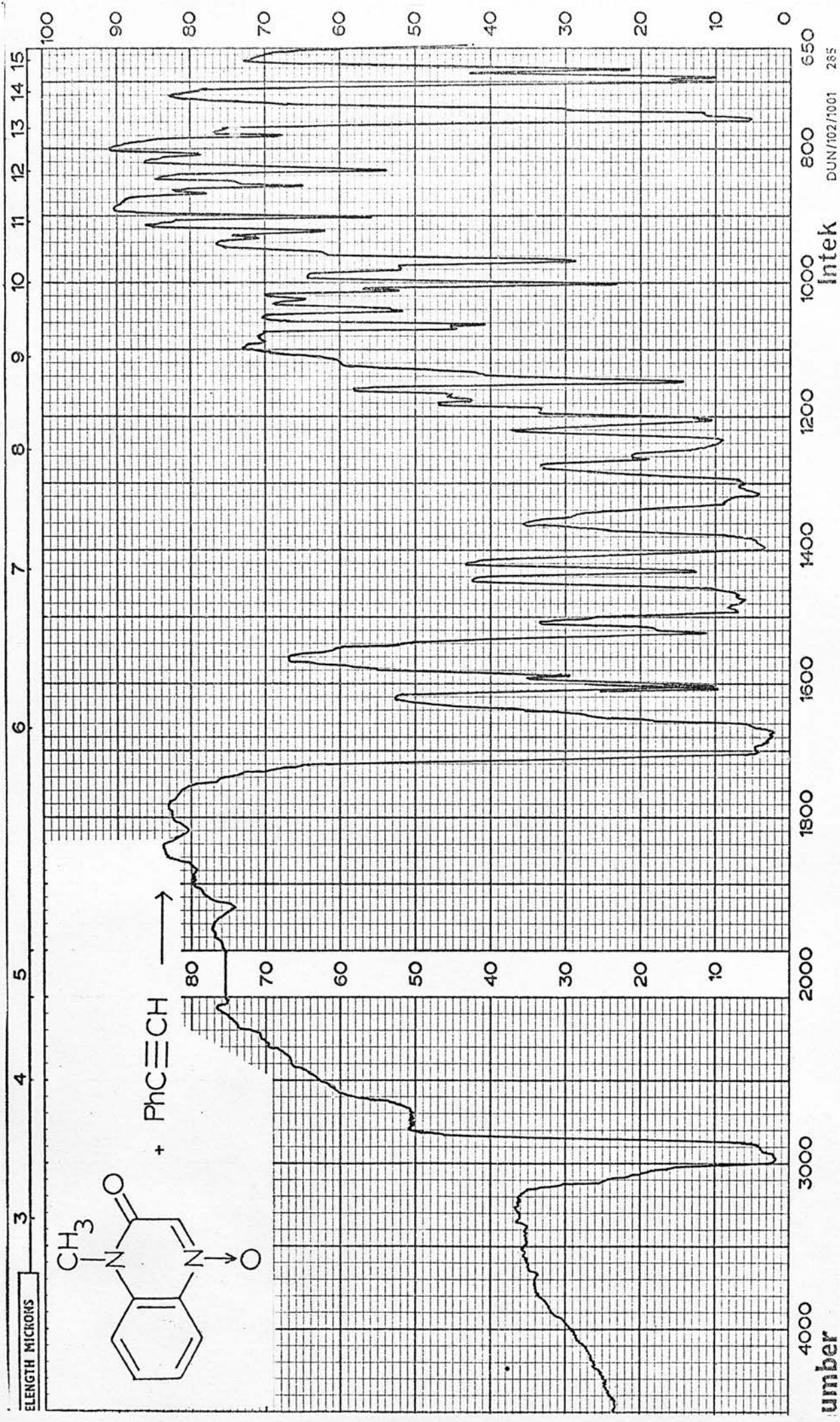


Figure 31.

spectrum, this white product is assigned the structure (293a). Thus it would appear that the tautomeric ketones (293a) and (294a) are capable of separate existence as discrete molecules. In an attempt to interconvert these tautomers the white ketone (293a) was warmed with 10% aqueous sodium hydroxide. However, it was recovered unchanged on acidification. Attempted methylation of the tautomer (293a) was unsuccessful and it may be significant that the reaction of the N-oxide (270b) with dibenzoylmethane afforded only the tautomeric form (294b). No trace was found of the alternative tautomer (293b).

The N-oxide (270a) when heated with phenylacetylene, in dry xylene, afforded two products, Y and Z, which were separable because of their differing solubilities. Neither solid was identical with either of the tautomeric ketones (293a) or (294a), nor did they show properties expected for the aldehyde (291a) which could result from addition of phenylacetylene across the nitron in the opposite direction. The mass spectrum of the more insoluble of the two products, (Y), indicated that its molecular weight was twice that expected for either of the ketones (293a) or (294a). However, the elemental analysis did not fit a dimeric structure. The ¹H n.m.r. spectrum of this compound contains two singlets in the olefinic region. The more soluble product, (Z), has the molecular formula, $C_{16}H_8N_2O_2$ and possesses only aromatic protons. Chromic acid oxidation of this compound afforded quinoxalin-2,3-(1H,4H)-dione (297), showing that it still retains the quinoxaline nucleus.

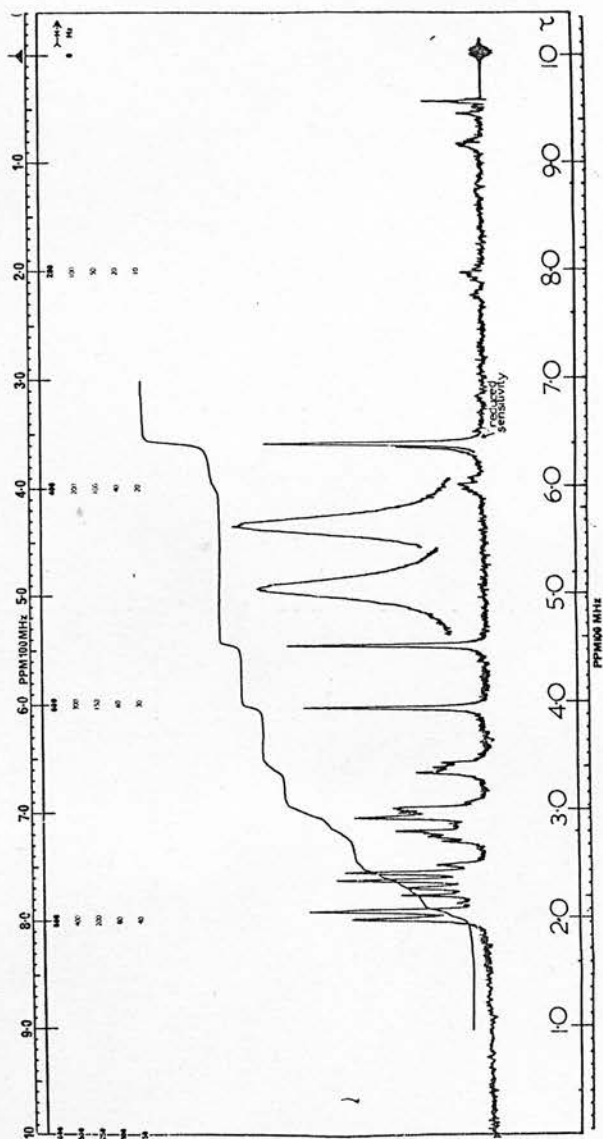


Figure 32. ^1H n.m.r. spectrum of compound X in trifluoroacetic acid at 100 MHz; inset expansion to 250 kHz.

The N-oxide (270b) reacted with phenylacetylene to give only one solid product, X, which was not identical with the ketone (294b). Its i.r. spectrum (Figure 31) showed that possibly several carbonyl groups were present and its ^1H n.m.r. spectrum (Figure 32) contains two singlets in the olefinic region. The molecular weight (556) of this product again indicates a dimeric structure and shows that each of the singlets in the ^1H n.m.r. spectrum are equivalent to two protons. Thus the product could be a symmetrical dimer and these peaks could each correspond to a single uncoupled olefinic proton. Alternatively, if the product is unsymmetrical, these signals could indicate the presence of two different methylene groups in the molecule.

In order to solve the structural problem posed by the products X and Y, degradation was attempted. However, compound X was stable to reduction with sodium dithionite, iron filings in acetic acid or catalytic hydrogenation, showing that the oxygen present in the molecule is not there in the form of an N-oxide group. The compound, X, was also stable to heating with 20% (w/v) aqueous sulphuric acid, and was recovered essentially unchanged on heating with 10% aqueous sodium hydroxide. Heating with potassium hydroxide in trigol resulted in decomposition to a dark oil, shown by T.L.C. to contain at least six components. Chromic acid oxidation of X afforded a product which was not a recognisable molecule and whose elemental analysis could not be fitted to a molecular formula.

This is the stage at which this problem now stands. Having met with little success, the broad degradative approach initially attempted, will have to be modified. Until such time as further work can be done in this direction no positive structural assignments can be made for the products obtained from the N-oxides (270a-b) and phenylacetylene.

SECTION FOUR

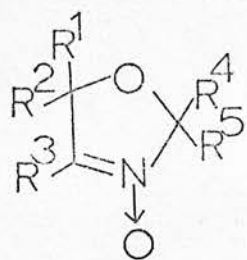
SOME STUDIES ON THE SYNTHESIS AND 1,3-DIPOLAR
CYCLOADDITION REACTIONS OF OXAZOLE 3-N-OXIDES

SOME STUDIES ON THE SYNTHESIS AND 1,3-DIPOLAR CYCLO-
ADDITION REACTIONS OF OXAZOLE 3-N-OXIDES

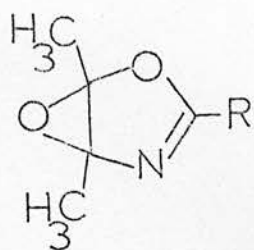
STUDIES OF THE DIELS-DILTHEY SYNTHESIS OF OXAZOLE 3-N-OXIDES

Many synthetic routes are available for the preparation of oxazoles but oxazole 3-N-oxides are more difficult to obtain and hence have been little studied. Unlike many other ring systems, oxazoles do not readily form N-oxides on treatment with peracids. An example has recently been recorded¹⁸⁰ of the formation of 3-oxazoline N-oxides (298) by treatment of the corresponding base with m-chloroperbenzoic acid. However, oxazole 3-N-oxides have apparently not been prepared in this way. Some oxazole 3-N-oxides are relatively unstable and would presumably break down on attempted synthesis from the oxazole by peracid oxidation. The only known synthetic route to oxazole 3-N-oxides involves the condensation of α -oximino ketones with aldehydes in the presence of hydrogen chloride. This method was first employed by Diels and Riley¹⁸¹ and subsequently extended by Dilthey and Friedrichsen.¹⁸² However, these authors formulated the products of the condensation of biacetyl monoxime with aryl aldehydes as the epoxides (299) rather than N-oxides. Cornforth and Cornforth¹⁸³ later suggested that these compounds had the oxazole 3-N-oxide structure (301). The correctness of the N-oxide formulation¹⁸³ has since been established by i.r. and u.v. spectral evidence and chemical behaviour.¹⁸⁴

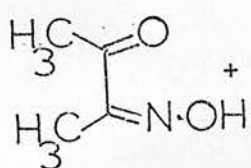
The oxazole 3-N-oxide (301a) had been shown to react with phenyl isocyanate but the structure of the product was



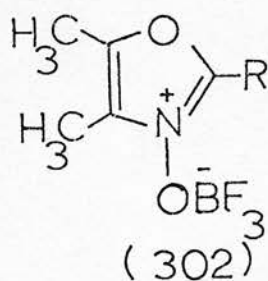
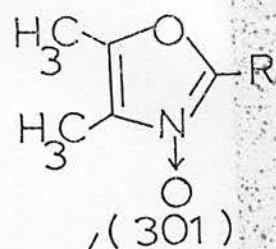
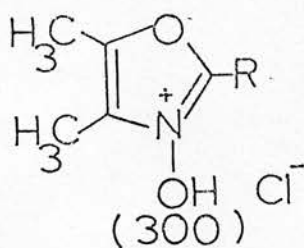
(298)



(299)



+ R·CHO



R

- (a) Ph
- (b) p-Cl·C₆H₄
- (c) p-OCH₃·C₆H₄
- (d) p-CH₃·C₆H₄
- (e) o-OH·C₆H₄
- (f) m-NO₂·C₆H₄
- (g) p-NO₂·C₆H₄
- (h) p-N(CH₃)₂·C₆H₄
- (j) CH₃

in dispute.^{181,183} Because of our interest in 1,3-dipolar cycloaddition reactions (see Section 3) it was decided to reinvestigate the reactivity of oxazole 3-N-oxides towards dipolarophiles such as phenyl isocyanate and if possible to establish unequivocally the structure of the products.

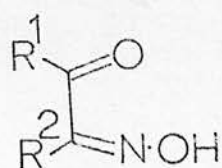
Although the synthesis of oxazole 3-N-oxides, described above, was well documented, its use appeared to be restricted to the preparation of 2-aryl-4,5-dialkyloxazole 3-N-oxides such as (301). Recently, however, it has been reported¹⁸⁵ that condensation of α -oximino ketones such as (303j) with benzaldehyde affords 4-acetyloxazole 3-N-oxide hydrochlorides. However the free N-oxides were not obtained in these instances. It was thus of interest to investigate the application of the Diels-Dilthey oxazole N-oxide synthesis to aliphatic aldehydes and other oximino derivatives.

Biacetyl monoxime condensed readily with substituted benzaldehydes in the presence of hydrogen chloride to give the oxazole 3-N-oxides (301). The N-oxides (301a-e) were isolated as their hydrochlorides (300a-e) by diluting the reaction mixture with ether. Treatment of these hydrochlorides with dilute ammonium hydroxide readily afforded the free N-oxides (301a-e). It was found that these N-oxides formed hydrates, convertible to the free N-oxides by storage over phosphorus pentoxide. As previously reported¹⁸² the oxazole 3-N-oxides (301a), (301c) and (301e) were sensitive to light and air, tending to discolour and decompose to gums. The previously unreported N-oxides (301b) and (301d) behaved similarly. Satisfactory analytical data could not be obtained

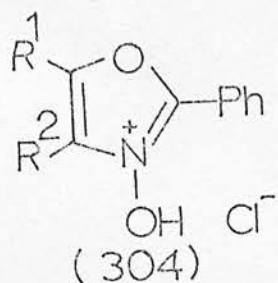
for the p-tolyl derivative (30ld) presumably due to its instability in air. The i.r. spectra and ^1H n.m.r. spectra (Table 7) of the N-oxides (30lb) and (30ld) were in accord with the assigned structures.

The m-nitro- and p-nitrophenyl derivatives (30lf-g) were obtained directly from the reaction mixture by dilution with water,¹⁸² no hydrochlorides being formed in these cases. The reaction mixture from the condensation of p-N,N-dimethylaminobenzaldehyde and biacetyl monoxime had to be evaporated and treated with ether to afford the hydrochloride (300h). Careful trituration and stirring with dilute ammonium hydroxide was employed to generate the free N-oxide (30lh) from the hydrochloride (300h). Trace amounts of unreacted aldehyde were detected in the ^1H n.m.r. spectrum of the crude product and were removed by crystallisation.

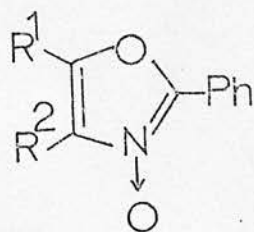
In an attempt to extend this synthetic method to aldehydes other than aromatic aldehydes, biacetyl monoxime was reacted with acetaldehyde in the presence of hydrogen chloride. The i.r. spectrum of the solid product indicated that it was a hydrochloride and the ^1H n.m.r. spectrum (Table 7) contained signals at τ 7.14, 7.57 and 7.68 due to three non-equivalent methyl groups. The product was unstable to crystallisation but on the basis of its spectral properties it is formulated as 2,4,5-trimethyloxazole 3-N-oxide hydrochloride (300j). Attempts to convert the hydrochloride (300j) by treatment with a variety of bases (dilute ammonia, sodium bicarbonate, sodium acetate) into the N-oxide (30lj) were either unsuccessful or afforded gums containing several



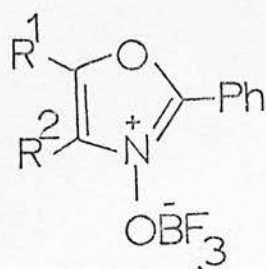
(303)



(304)

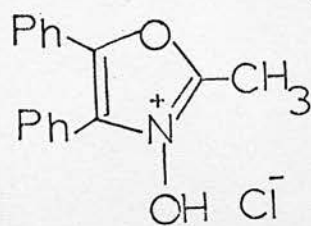


(305)

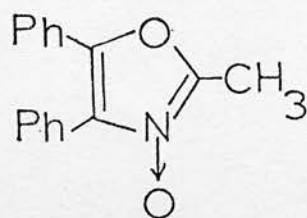


(306)

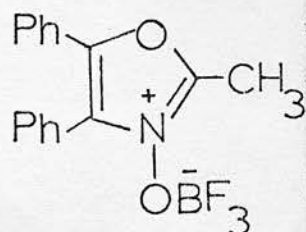
	R^1	R^2
(a)	Ph	CH_3
(b)	CH_3	Ph
(c)	Ph	H
(d)	CH_3	H
(e)	Ph	CN
(f)	CH_3	CO_2Et
(g)	CH_3	CO_2H
(h)	Ph	CO_2Et
(j)	CH_3	COCH_3
(k)	C_2H_5	CH_3



(307)



(308)



(309)

components. Attempts to form stable adducts of the N-oxide (301j) by treating the hydrochloride (300j) with picric acid or boron trifluoride etherate were also unsuccessful. Thus it would appear that, although the condensation of biacetyl monoxime with aromatic aldehydes is a general reaction, the presence of at least one aromatic ring is essential to the stability of the N-oxide product.

The effect of varying the oxime component while keeping the aldehyde component constant was next studied by condensing a series of oximino compounds (303) with benzaldehyde in the presence of hydrogen chloride.

The oximino compound (303a) readily formed the 4-methyl-5-phenyloxazole 3-N-oxide (305a)¹⁸² but as reported by Dilthey and Friedrichsen¹⁸² the isomeric oximino compound (303b) afforded a dark, intractable oil rather than the corresponding N-oxide (305b) which is presumably unstable in the reaction medium.

The application of the Diels-Dilthey synthesis to the preparation of oxazole 3-N-oxides unsubstituted in the 4-position was largely unsuccessful. Condensation of 2-oximinoacetophenone (303c) with benzaldehyde in the presence of hydrogen chloride afforded a solid product but in insufficient amount for characterisation. The ¹H n.m.r. spectrum was unrevealing due to the signal overlap in the aromatic region. However the product is assigned the N-oxide structure (305c) since its i.r. spectrum was identical with the compound obtained by treating the boron trifluoride adduct (306c) with sodium dithionite (see later). The oximino

compound (303d) reacted with benzaldehyde to afford a hygroscopic, pale yellow solid. The hydrochloride structure (304d) for this product is supported by its i.r. and ^1H n.m.r. spectra. However, attempts to liberate the free N-oxide (305d) from the hydrochloride (304d) or to convert it into a stable boron trifluoride adduct were unsuccessful.

An attempt was next made to adapt the Diels-Dilthey synthesis for the preparation of oxazole 3-N-oxides possessing a functional group at C(4). Attempted condensation of the oximino cyano-compound (303e) with benzaldehyde was, however, unsuccessful and resulted in recovery of the starting material. The oximino ester (6f) reacted readily with benzaldehyde in the presence of hydrogen chloride to afford a hygroscopic hydrochloride (304f) which could not be converted into the N-oxide (305f) by treatment with dilute ammonium hydroxide. However, treatment with sodium acetate afforded the N-oxide (305f) as a white solid. The i.r. and ^1H n.m.r. spectra (Table 1) of the compounds (304f) and (305f) were in accord with the assigned structures. However, the N-oxide (305f) was very unstable and rapidly decomposed to a yellow gum on standing for a short time at room temperature. The ^1H n.m.r. spectrum of this gum indicated that several components were present and that the N-oxide (305f) decomposed too rapidly to be studied further. Immediate analysis of this N-oxide gave analytical data in accord with the structure (305f). Also, immediate treatment of a solution of the N-oxide (305f) in acetic acid with boron trifluoride etherate afforded a stable boron trifluoride adduct (306f).

Hydrolysis of the hydrochloride (304f) by warming briefly with 10% aqueous sodium hydroxide afforded the corresponding carboxylic acid (305g) which, unlike the ester (305f), was a stable molecule. In contrast to (303f), the oximino compound (303h) failed to react with benzaldehyde in the presence of hydrogen chloride. The poor yield of oxazole N-oxide obtained from (303c) and the failure of the oximino compounds (303e) and (303h) to react at all, demonstrates the lower reactivity of a benzoyl group relative to an acetyl group.

Although the N-oxide (301j) from biacetyl monoxime and acetaldehyde could only be isolated as the crude hydrochloride (300j), it was thought that the stabilising effect of the two phenyl groups in benzil monoxime would permit extension of the hydrogen chloride method to include acetaldehyde and hence the synthesis of the 2-methyl-N-oxide (308). However, this N-oxide was only obtained in a crude form as its hydrate. Attempted crystallisation caused decomposition and after drying in vacuo over phosphorus pentoxide, exposure to air caused immediate decomposition to a gum which yielded benzil on trituration with cold, aqueous sodium hydroxide.

From these results it can be seen that whilst some success was achieved in extending the Diels-Dilthey synthesis, the low yields obtained and the difficulties encountered in the isolation of the free N-oxides (305) show that this synthetic route to oxazole 3-N-oxides is relatively inflexible.

In the light of the observation that the N-oxide (305f) formed a stable boron trifluoride adduct (306f) it was decided

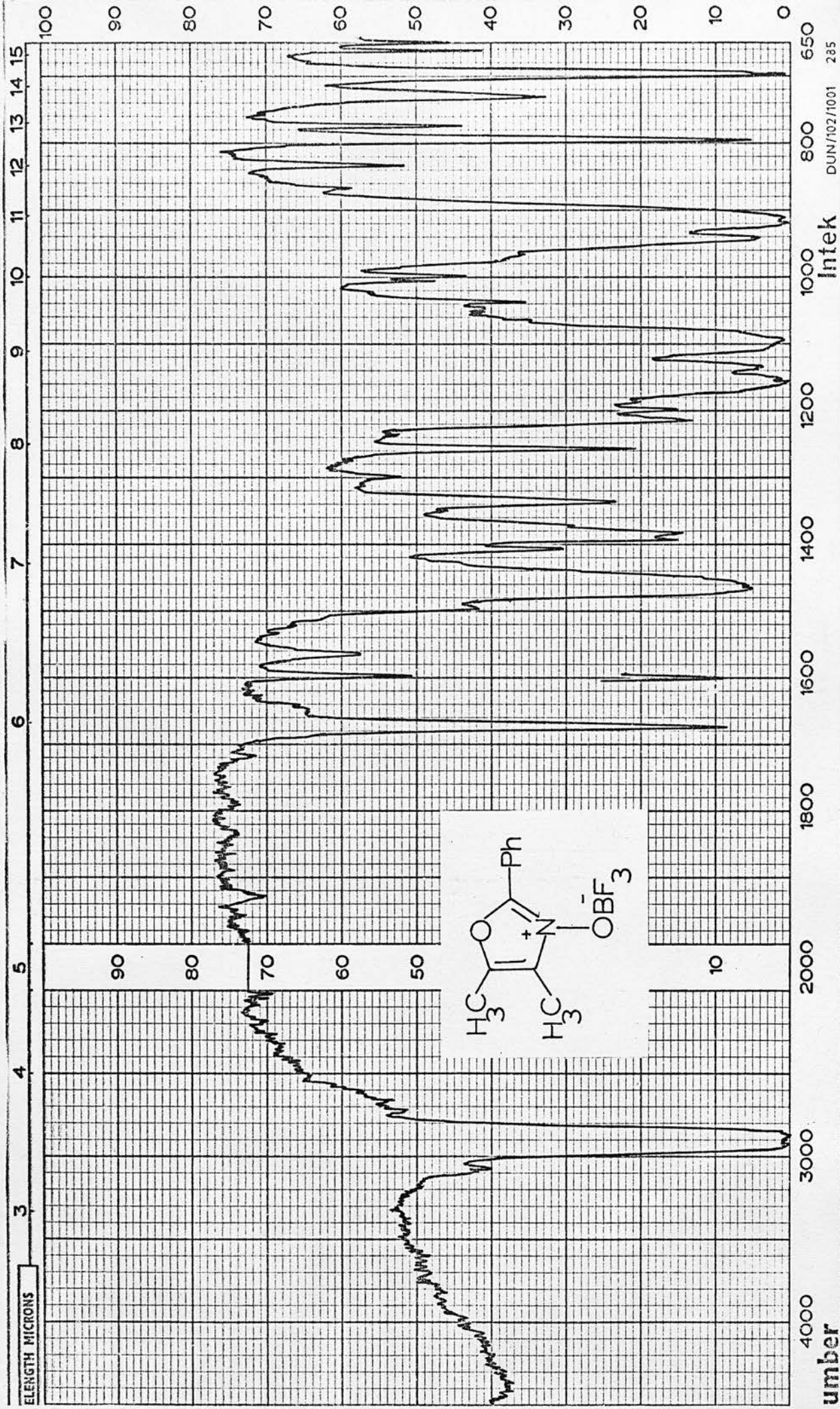


Figure 33

to examine the formation of this type of adduct from oxazole 3-N-oxides. Many types of heterocyclic N-oxide form boron trifluoride adducts.^{15,16} The stability of these adducts can vary somewhat but generally they are readily reconverted into the corresponding N-oxides. This was shown to be the case for the quinoxalin-3(4H)-one 1-N-oxide boron trifluoride adduct (249) which reverted to the N-oxide (216a) on attempted crystallisation. The N-oxide (301a), when treated with boron trifluoride etherate afforded a white crystalline solid whose mass spectrum showed a parent ion corresponding to the N-oxide (301a) though small peaks at m/e 10 and m/e 11 showed the presence of boron. Also, the i.r. spectrum (Figure 33) was not identical with that of the N-oxide (301a) and the ^1H n.m.r. spectrum (Table 1) and elemental analysis were in accord with its formulation as the adduct (302a). The adduct (302a) was stable to crystallisation from acetic acid but on heating with ethanol afforded a solid shown by its ^1H n.m.r. spectrum to be a complex mixture. The N-oxide (305a) likewise afforded a boron trifluoride adduct (306a) in quantitative yield. As previously mentioned, no adducts could be formed by treating the hydrochlorides (300j) and (304d) with boron trifluoride etherate.

The formation of stable boron trifluoride adducts from oxazole 3-N-oxides prompted a study of the condensation of oximino compounds with aldehydes using boron trifluoride as catalyst. Biacetyl monoxime and the oximino compounds (303a) and (303f) condensed readily with benzaldehyde in the presence of boron trifluoride to afford the corresponding

oxazole 3-N-oxide boron trifluoride adducts (302a), (306a) and (306f) in good yield. These adducts were identical with the products obtained by treating the corresponding N-oxides directly with boron trifluoride. The oximino compounds (303e) and (303h) which failed to react in the presence of hydrogen chloride, condensed with benzaldehyde in the presence of boron trifluoride to form the adducts (306e) and (306h). However, the yields of these adducts were low. The oximino compound (303b) which afforded an intractable oil by the hydrogen chloride method, condensed with benzaldehyde in the presence of boron trifluoride to yield the adduct (306b). The reaction time had to be kept relatively short, in this case, as decomposition occurred in the reaction medium. The use of boron trifluoride as catalyst did little to enhance the yield of the condensation of (303c) with benzaldehyde, the adduct (306c) being formed only in moderate yield. Although the oxazole 3-N-oxide hydrochlorides (300j) and (304d) could not be converted into the corresponding boron trifluoride adducts (302j) and (306d), the latter compounds were obtained by condensation of the corresponding oximino and aldehyde components in the presence of boron trifluoride. Similarly, benzil monoxime and acetaldehyde condensed in the presence of boron trifluoride to yield the adduct (309) which could not be formed directly from the N-oxide (308). The attempted condensation of the oximino compound (303j) with benzaldehyde in the presence of boron trifluoride afforded an intractable oil and was the only instance of the reactions attempted which failed to give a solid product by this method.

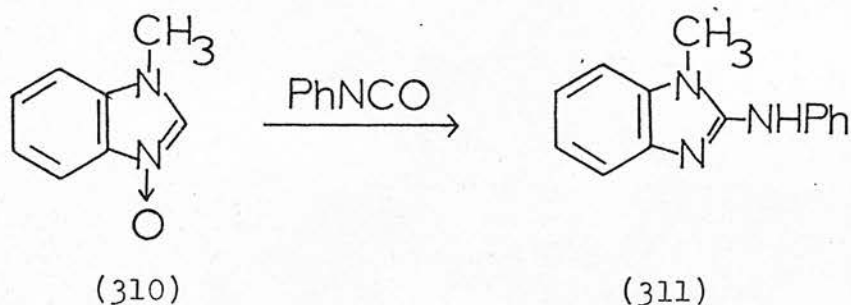
explain the rather surprising stability of the N-oxide group to dithionite reduction. Treatment of the boron trifluoride adduct (306a) with sodium dithionite similarly afforded the corresponding N-oxide (305a) but only a dark oil was obtained when this method was applied to the adduct (306b). Thus none of the methods studied is suitable for the synthesis of the N-oxide (305b). The 4-unsubstituted adduct (306c) reacted with sodium dithionite to afford a solid which was identical with that obtained by the hydrogen chloride method. This product decomposed on attempted crystallisation from benzene, but is assigned the N-oxide structure (305c) on the basis of its spectral properties. The small amount of solid obtained from the dithionite reduction of the adduct (306e) was insufficient for characterisation but did not appear to be the cyano-N-oxide (305e) since the i.r. spectrum contained absorption due to an amino-group.

In view of these latter results it is apparent that the boron trifluoride method offers no great advantage over the use of hydrogen chloride in the preparation of oxazole 3-N-oxides. It does appear, however, that oximino compounds and aldehydes condense more readily in the presence of boron trifluoride.

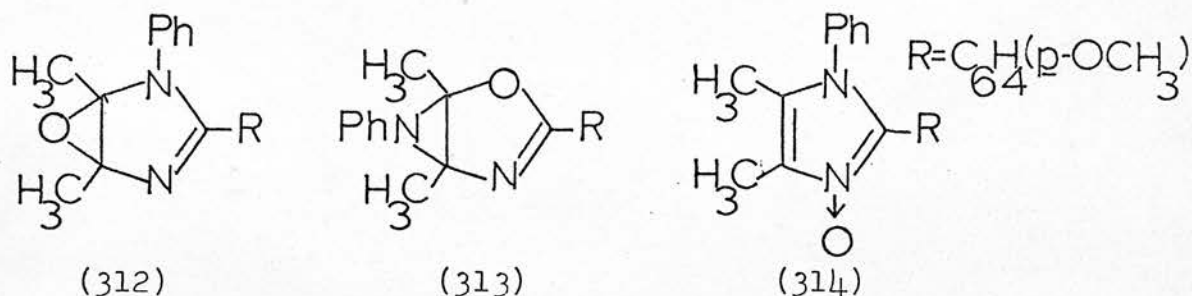
THE REACTIONS OF OXAZOLE 3-N-OXIDES WITH PHENYL ISOCYANATE

As described in the preceding Section, N-oxides having an adjacent unsubstituted position undergo 1,3-dipolar cycloaddition with phenyl isocyanate to afford 2-N-phenylamino derivatives such as (271). Relatively few examples of this

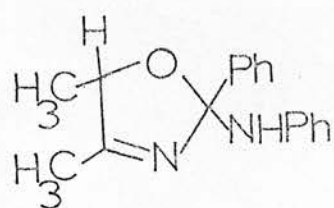
type of reaction are known in the case of azole N-oxides. Takahashi and Kano¹⁰² report the formation of 2-N-phenylamino-1-methylbenzimidazole (311) from 1-methylbenzimidazole 3-N-oxide (310) and phenyl isocyanate. In contrast, the corresponding reaction with 1,2-dimethylbenzimidazole 3-N-oxide (276) which is blocked at the 2-position is reported¹⁴⁴ to give the 6-N-phenylamino-derivative (277) (see Section 3, page 103).



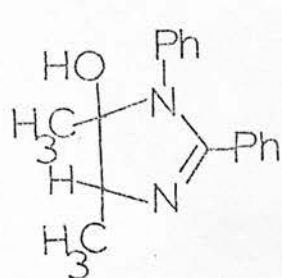
Diels and Riley¹⁸¹ were the first to examine the reaction of the 'oxidoöxazole' (299c) [which is now known to be the N-oxide (301c)] with phenyl isocyanate. They formulated the product obtained as either (312) or (313). This reaction was later examined by Cornforth and Cornforth¹⁸³ who assigned the structure (314) to the product.



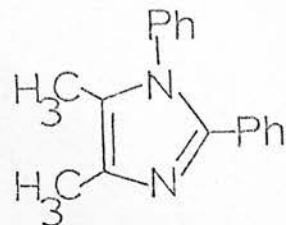
Since none of the structures was supported by firm experimental evidence, it was decided to investigate the reactions of oxazole 3-N-oxides with isocyanates with a view to determining



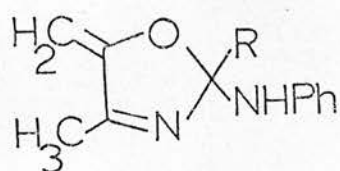
(319)



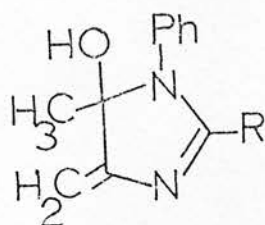
(320)



(321)



(315)



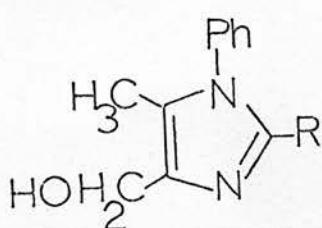
(316)

R
(a) Ph

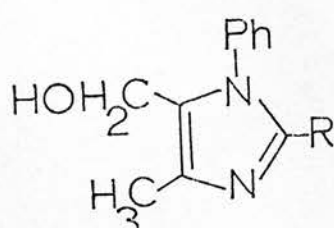
(b) p-Cl·C₆H₄

(c) p-OCH₃·C₆H₄

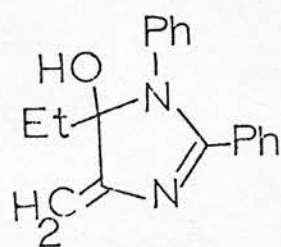
(d) p-CH₃·C₆H₄



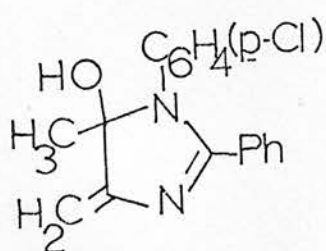
(322)



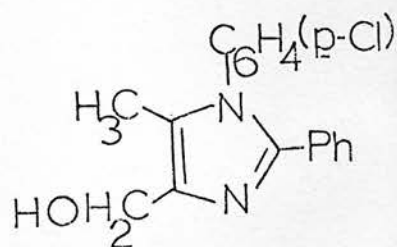
(323)



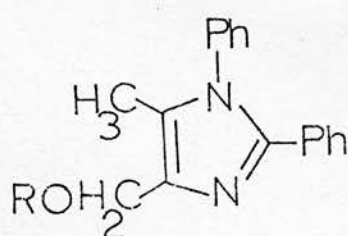
(324)



(325)

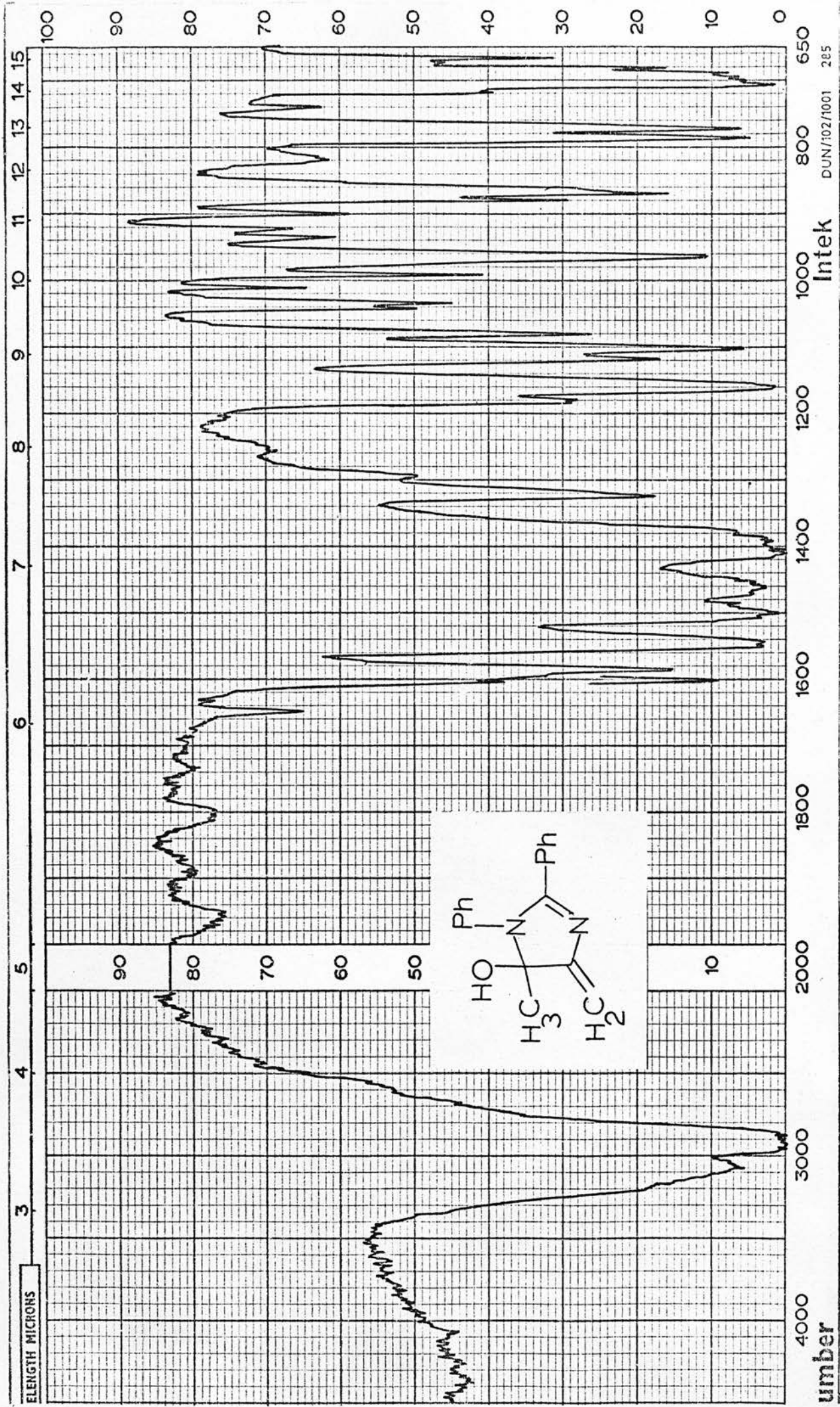


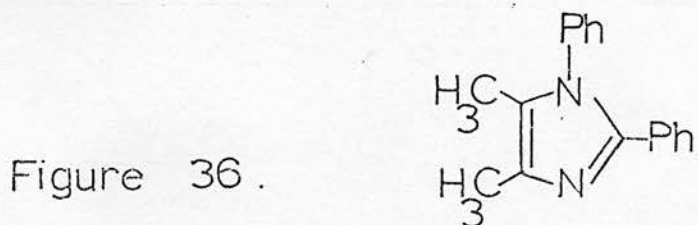
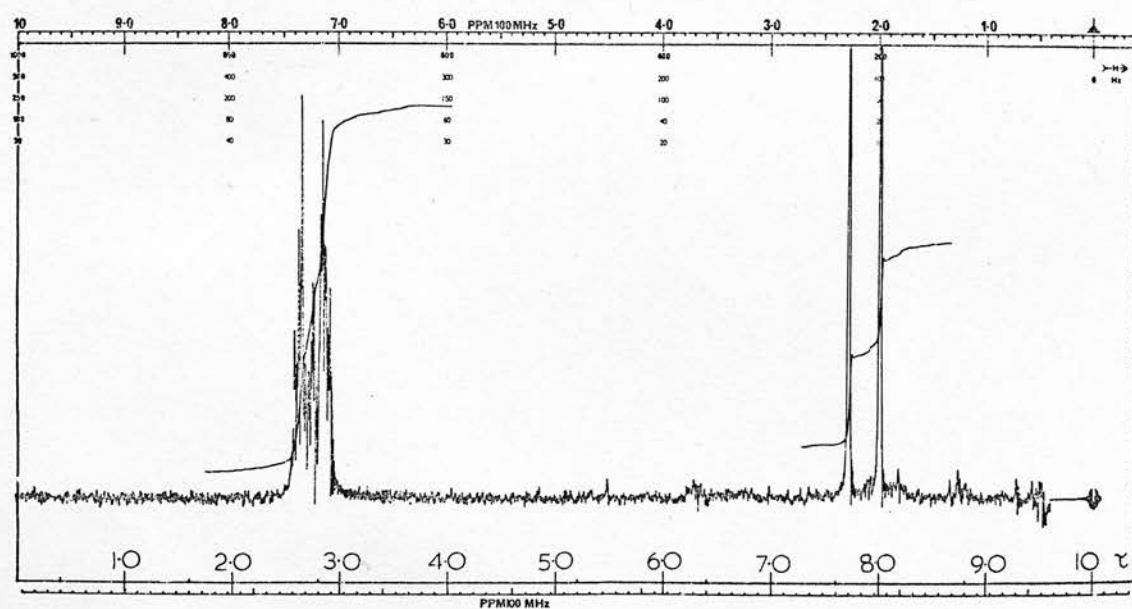
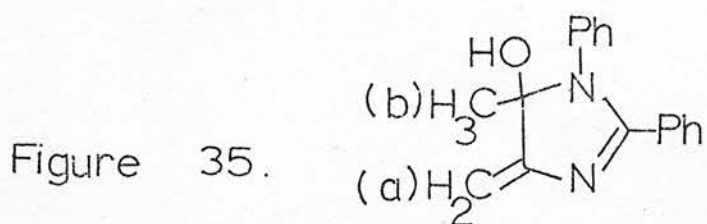
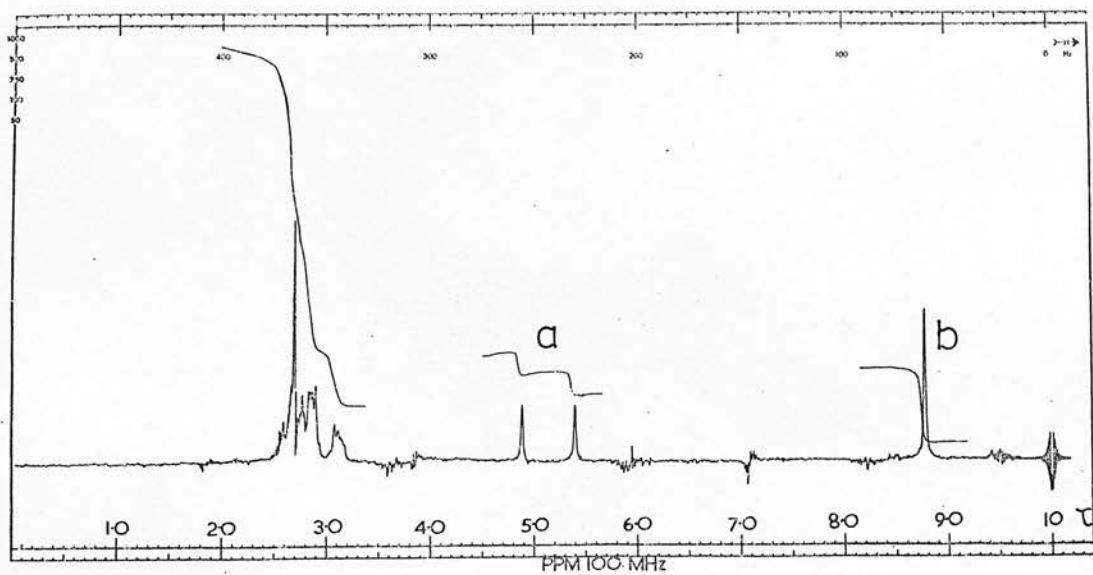
(326)



(327)

R
(a) Ac
(b) CH₃
(c) Et





^1H n.m.r. spectra of compounds (316a) (Figure 35) and (321) (Figure 36) at 100 MHz in deuteriochloroform.

the structures of the products.

Reaction of 4,5-dimethyl-2-phenyloxazole 3-N-oxide (30la) with phenyl isocyanate occurred readily at room temperature with evolution of heat and gas. The white crystalline solid isolated from this reaction gave analytical data consistent with the molecular formula $C_{17}H_{16}N_2O$. This formula implies addition of phenyl isocyanate to the 3-N-oxide (30la) and subsequent loss of carbon dioxide. Examination of the 1H n.m.r. spectrum of the product (Table 8 and Figure 35) showed the presence of only one methyl signal thus excluding the previously assigned structures (312), (313) or (314). The spectrum also contains two singlets at τ 4.89 and 5.40 each integrating for one proton. This type of absorption is characteristic of a terminal methylene group.¹⁸⁶ Thus, at this stage it can be presumed that either the 4- or 5-methyl group of the starting oxazole 3-N-oxide (30la) has been transformed into a terminal methylene group. The i.r. spectrum of the product (Figure 34) possessed no carbonyl group and thus the oxygen atom in the product must be in a closed ring structure or in a hydroxyl group. On the evidence thus far two possible structures can be written for the product. 1,3-dipolar cycloaddition of phenyl isocyanate followed by abstraction of a hydrogen atom from the 5-methyl group and liberation of carbon dioxide as shown in Scheme 12 would give rise to the Δ^4 -oxazoline (315). Structures of a similar type are known.¹⁸⁰ However a structure of the type (315a) would be expected to be relatively unstable due to the presence of the imino-ether group.

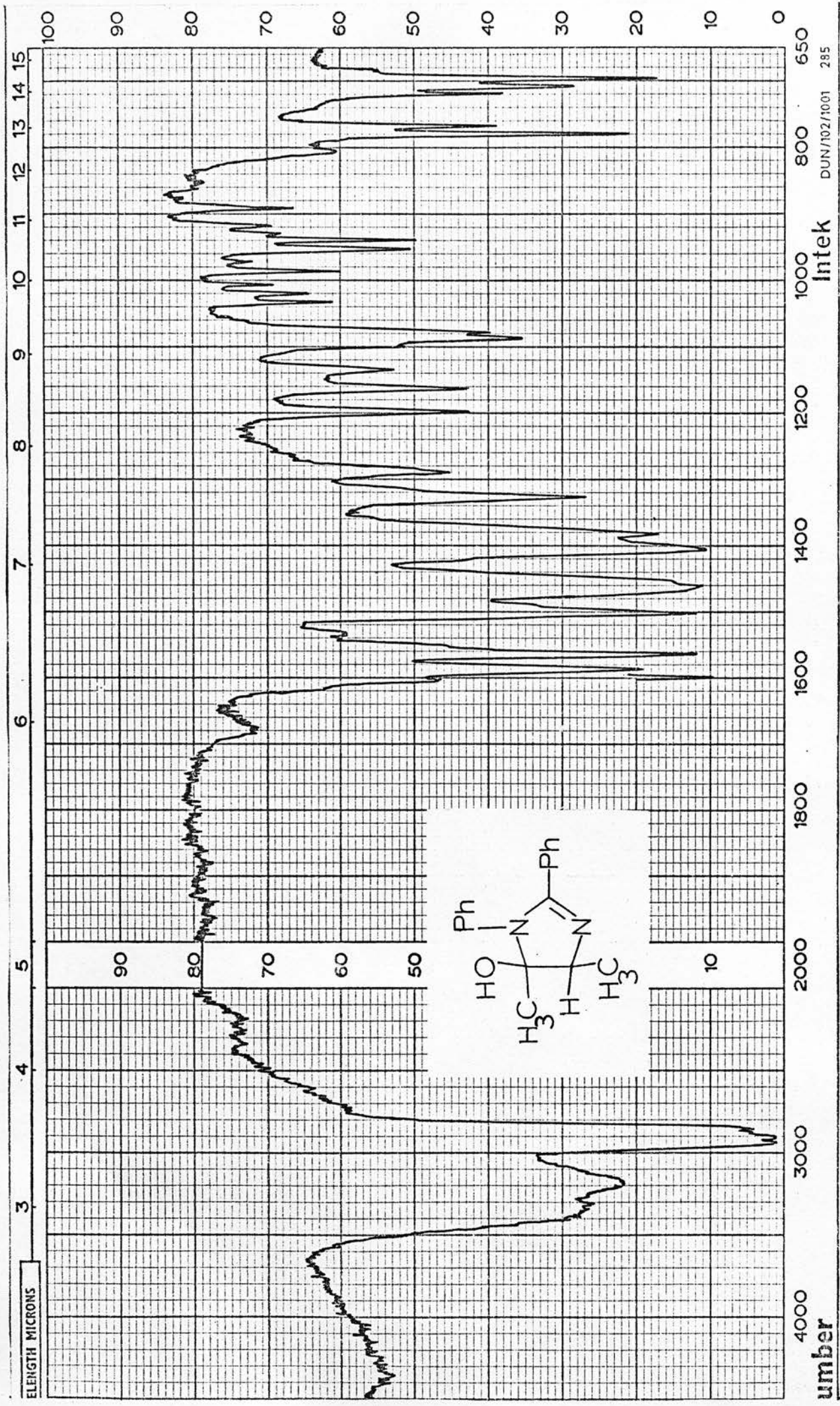
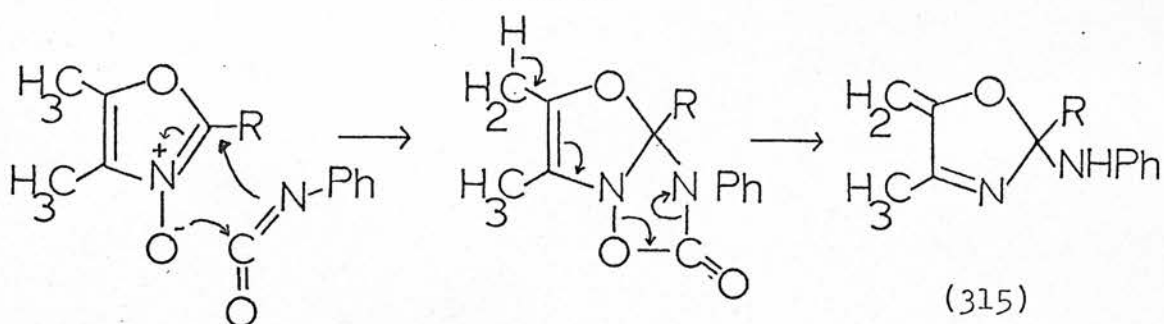


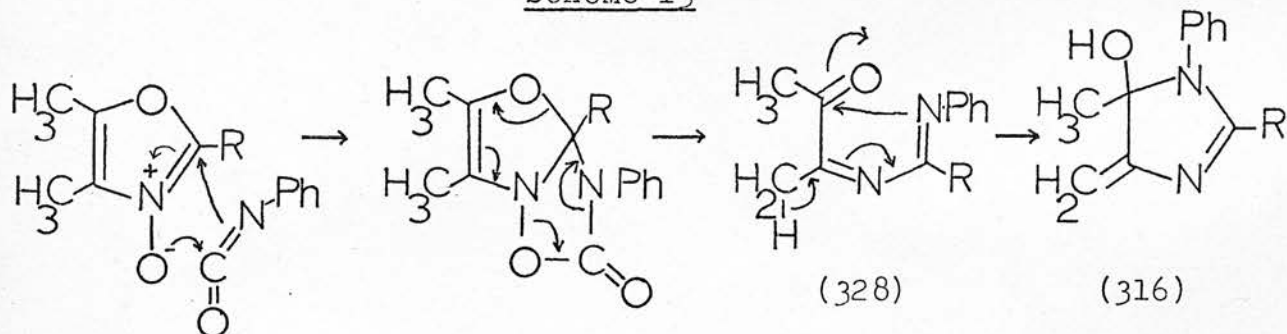
Figure 37.

Scheme 12



Alternatively, opening of the oxazole ring followed by re-cyclisation, as shown in Scheme 13 could give rise to the imidazole derivative (316a). Both structures (315a) and (316a) fit the spectral properties observed for the product and thus no distinction can be made between them without further evidence.

Scheme 13



The presence of the terminal methylene group was further established by catalytic hydrogenation. One equivalent of hydrogen was taken up and the i.r. spectrum of the product (Figure 37) still contained no carbonyl group suggesting that any ring in the molecule had remained intact. The signals due to the terminal methylene group in the ^1H n.m.r. spectrum (Figure 38) of the adduct (315a) or (316a) were replaced in the hydrogenated compound by a quartet centred at τ 5.93 integrating for one proton and a doublet centred

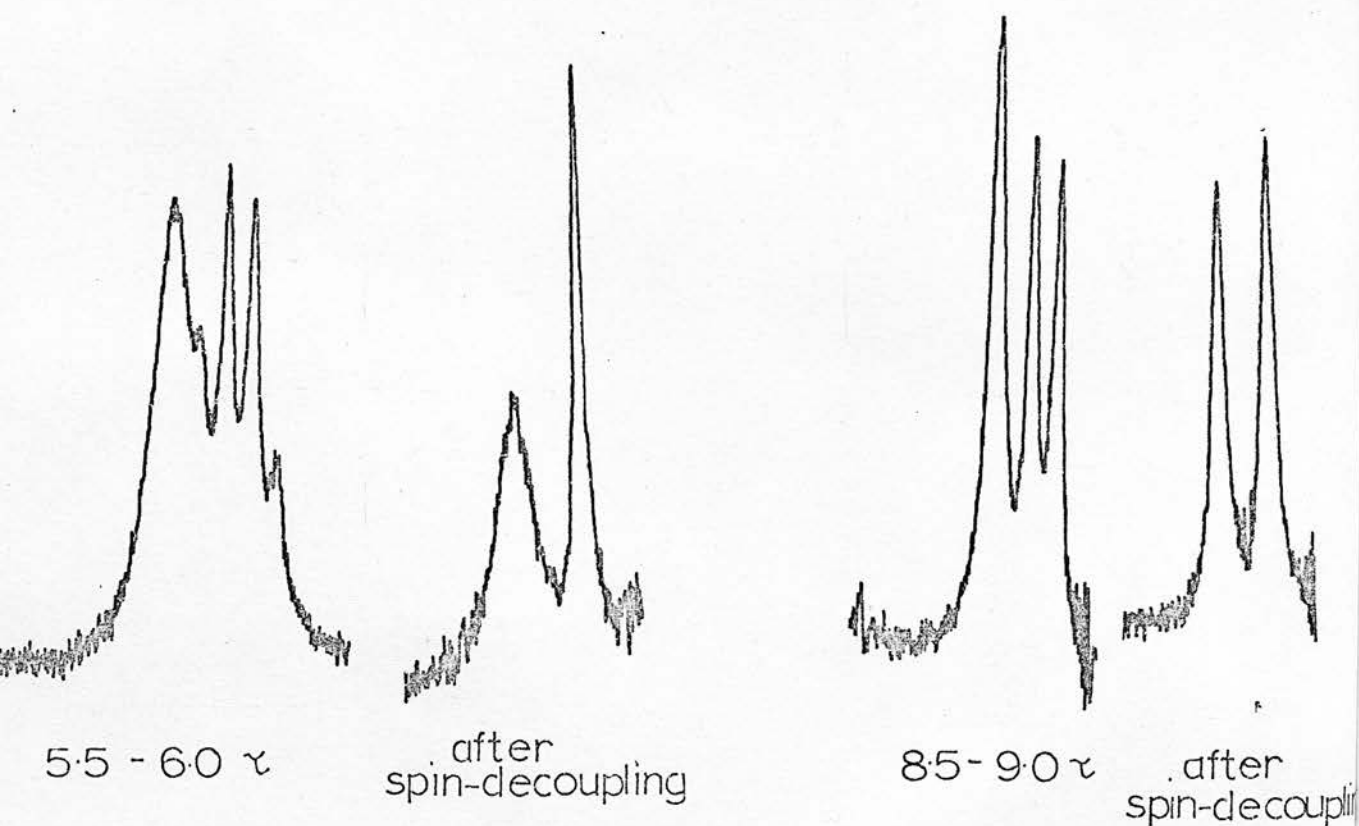
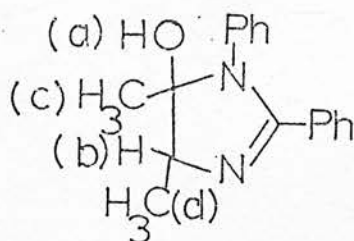
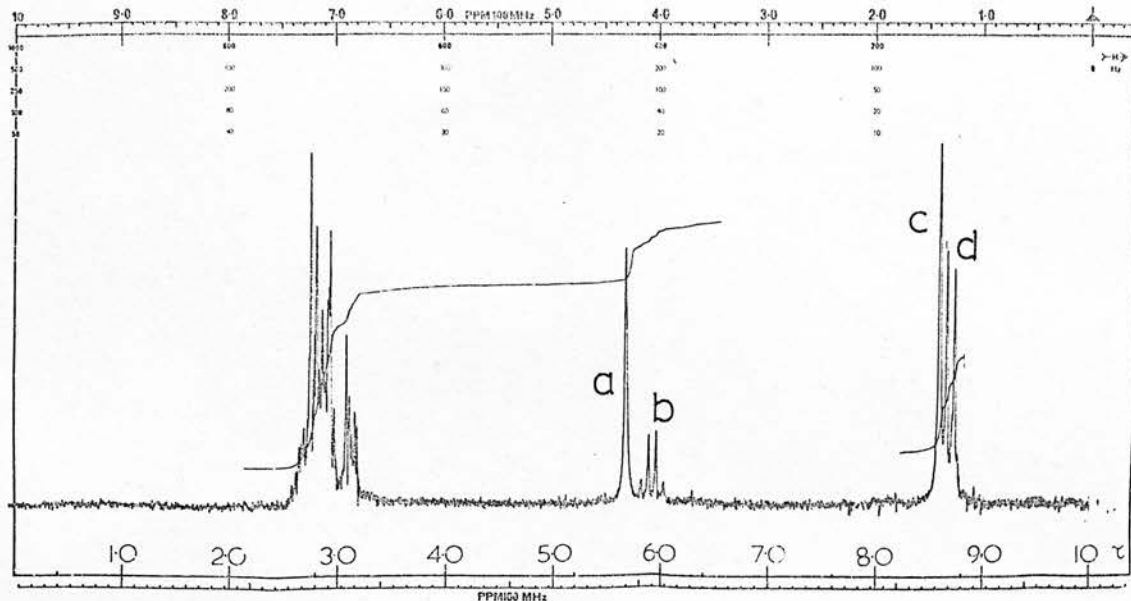
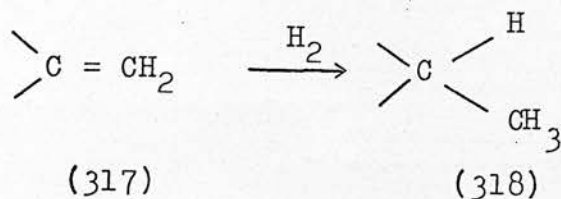


Figure 38.

^1H n.m.r. spectrum, plus spin-decoupling, of compound (320) at 100 MHz in deuteriochloroform.

at τ 8.71 integrating for three protons (see Figure 38). This suggested that the transformation (317) \rightarrow (318) had occurred.



Spin-decoupling confirmed that this was the case (see Figure 38). Irradiation at τ 5.93 resulted in the collapse of the doublet at τ 8.71 to a singlet, and irradiation at τ 8.71 caused the collapse of the quartet at τ 5.93 to a singlet. On the basis of this evidence either of the structures (319) or (320) can be assigned to the hydrogenation product. However, the presence of a singlet at τ 5.67 was thought more likely to be due to a hydroxyl group than a secondary amine thus favouring structure (320). Another point in favour of the structure (320) was that on standing in contact with ether, the hydrogenated compound (319) or (320) underwent dehydration. The product thus obtained analysed correctly for $\text{C}_{17}\text{H}_{16}\text{N}_2$, and the ^1H n.m.r. spectrum (Figure 36) contained signals (τ 7.73, 8.02) due to two methyl groups. It was thought likely, and later confirmed that the dehydration product was the imidazole derivative (321). Since it is unlikely that the oxazoline derivative (319) would rearrange and dehydrate simply on standing in contact with ether these results support the structures (320) and (316a) for the hydrogenation product and the phenyl isocyanate adduct. The attempted preparation of the imidazole derivative (321) by

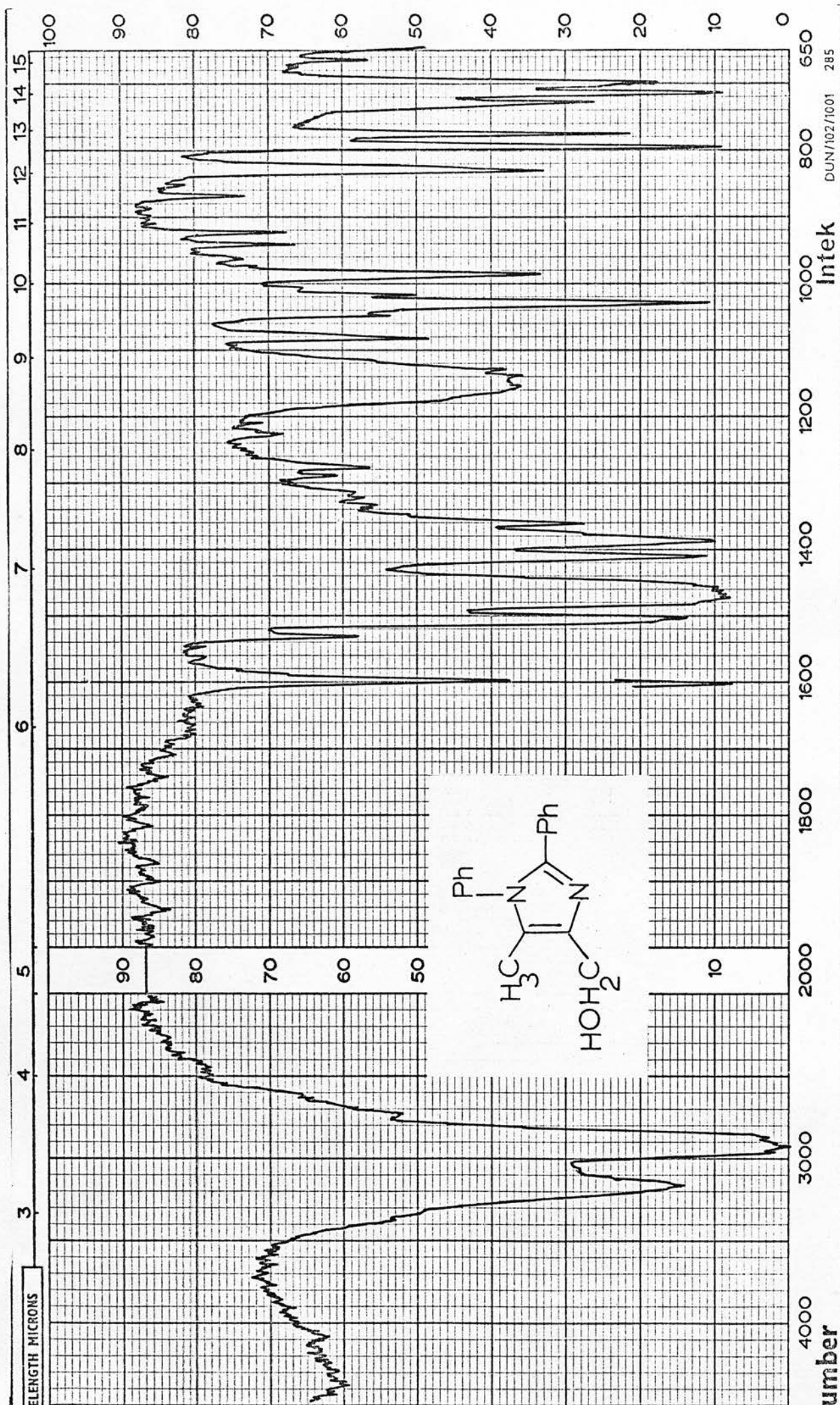
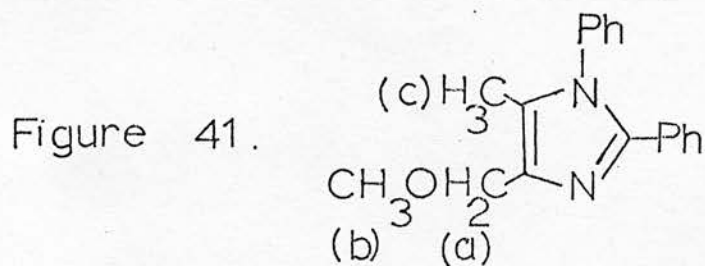
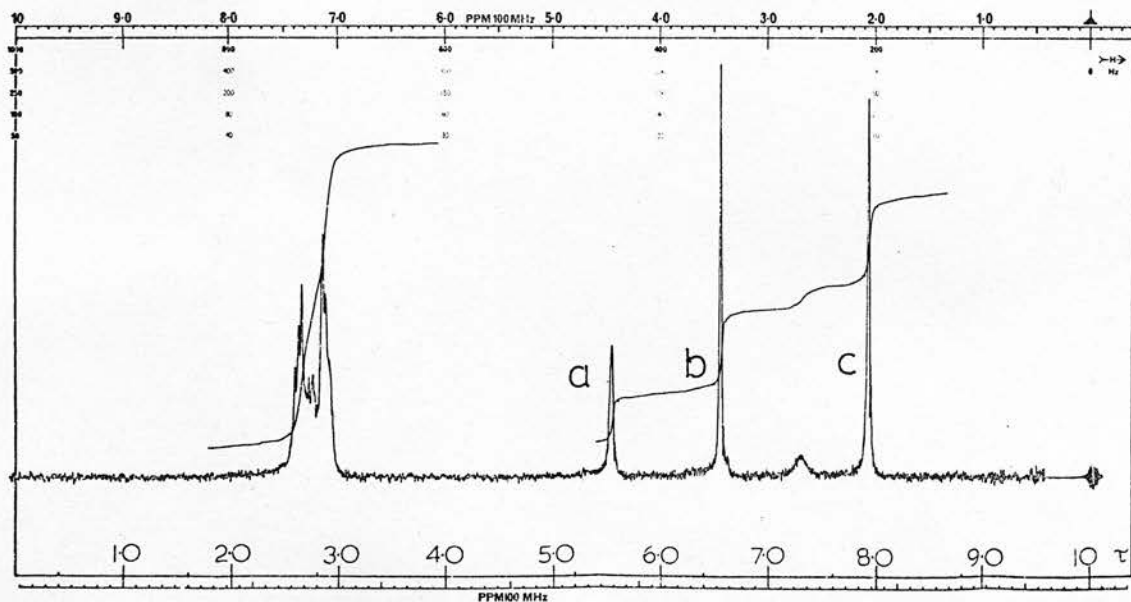
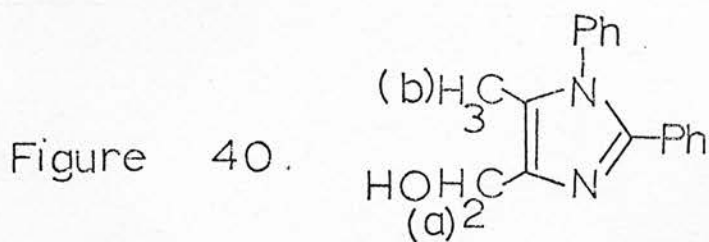
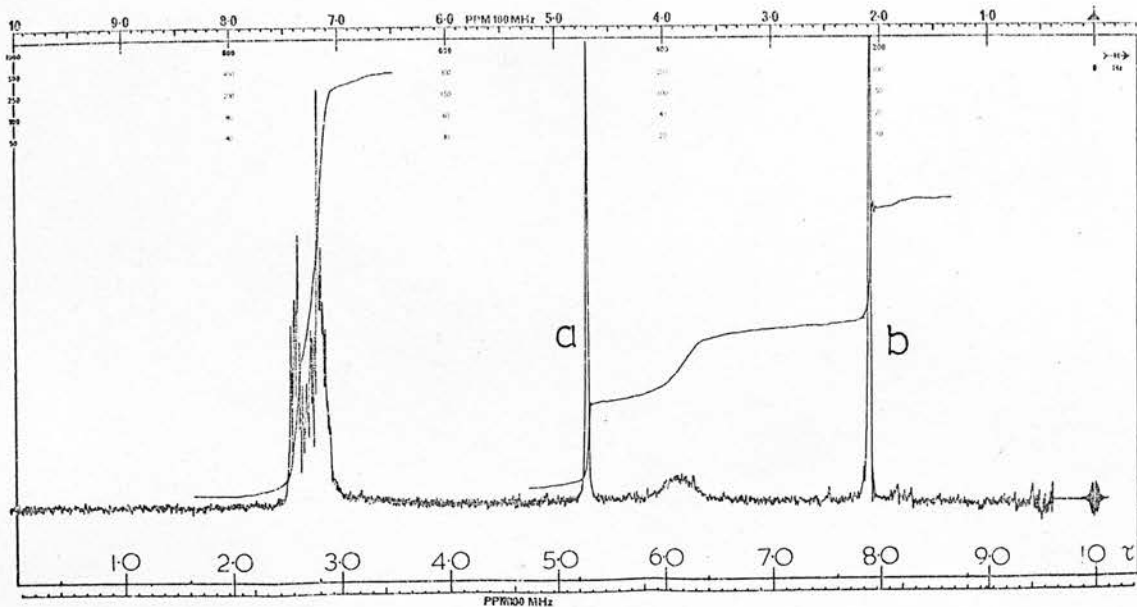


Figure 39.

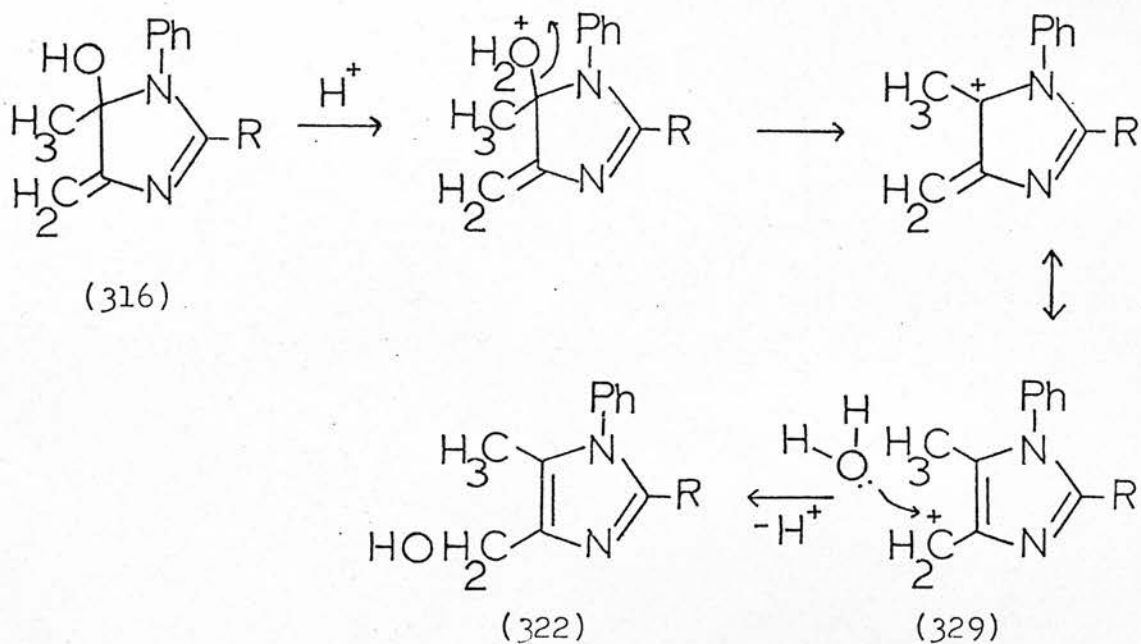
heating N-phenylbenzamidine with acetoin in ethanol, was unsuccessful.

The alkaline hydrolysis of the adduct (315a) or (316a) was carried out to see if further information on the structure could be obtained. No reaction occurred on leaving the adduct in contact with 10% aqueous sodium hydroxide in ethanol at room temperature for 24h. Heating under reflux in this medium for 30 min., however, caused complete degradation to a mixture of benzanilide, aniline and benzoic acid. In contrast, heating under reflux with N aqueous sodium carbonate had no effect on the adduct. This behaviour again tended to favour the structure (316a) as it is unlikely that the imino-ether (315a) would be stable to these basic conditions. On the other hand, degradation was too complete to afford positive evidence for the structure of the adduct.

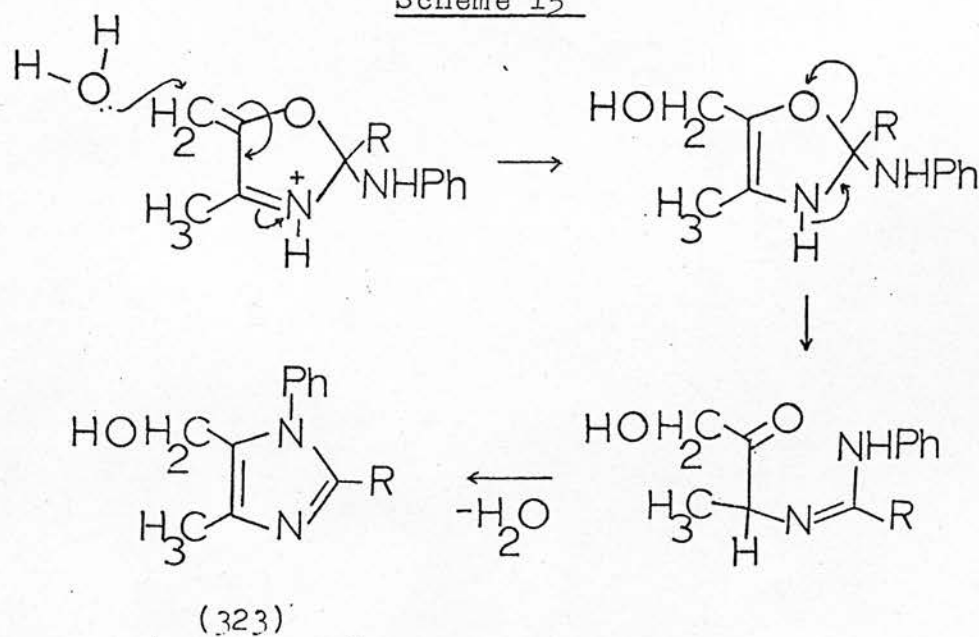
On warming for 30 min, with dilute sulphuric acid, the adduct (315a) or (316a) afforded an isomeric compound in high yield. Examination of the i.r. spectrum (Figure 39) and the ^1H n.m.r. spectrum (Figure 40 and Table 9) of this product indicated the presence of a hydroxymethyl group. This facile rearrangement can be readily explained, therefore, in terms of a simple allylic rearrangement of the imidazole derivative (316a) to the hydroxymethyl derivative (322a) (Scheme 14).



^1H n.m.r. spectra of compounds (322a) (Figure 40) and (327a) (Figure 41) at 100 MHz in deuteriochloroform.

Scheme 14

Alternatively a similar product (323a) could possibly be formed as shown in Scheme 15, from the Δ^4 -oxazoline structure (315a).

Scheme 15

The key difference between the possible products of rearrangement is that (322a) possesses a 4-hydroxymethyl-group whereas (323a) possesses a 5-hydroxymethyl-group. Unambiguous synthesis of either of the hydroxymethyl compounds (322a) or (323a) would therefore resolve the question of the structure of the product obtained from the N-oxide (301a) and phenyl isocyanate. While this approach was being considered, a paper was published by Goto et al.¹⁸⁷ in which they described the reaction of several oxazole 3-N-oxides with phenyl isocyanate and the subsequent acid-catalysed rearrangements and catalytic hydrogenation of the products obtained. The results obtained by Goto et al.¹⁸⁷ are in agreement with those obtained in the present study. These workers did not consider the possibility of the alternative structure (315). However this structure is excluded by the report by Goto et al.¹⁸⁷ that 5-ethyl-4-methyl-2-phenyloxazole 3-N-oxide (301k) reacts with phenyl isocyanate to give a product (324) still containing an ethyl group. This means that in the case of the N-oxide (301a) the 5-methyl group cannot be involved in the formation of the adduct. Consequently the structure (315a) for the adduct and (319) and (323a) for the hydrogenation product and hydroxymethyl compound are excluded. Consequently, as also proposed by Goto et al.¹⁸⁷ the product obtained by reaction of the N-oxide (301a) with phenyl isocyanate is the 4-methylene-4,5-dihydroimidazole (316a) which on treatment with acid isomerises to the 4-hydroxymethyl-imidazole (322a). It also follows that the structure (320) is correct for the hydrogenation product of the adduct

derived from (301a). The synthesis of 4,5-dimethyl-1,2-diphenylimidazole (321) described by Goto et al.¹⁸⁷ was repeated with a slight modification, to confirm that this compound was identical with the product obtained by catalytic hydrogenation of (316a) and subsequent dehydration (see before).

In addition to the 2-p-anisyl-N-oxide (301c) which is known^{181,183} to react with phenyl isocyanate, the 2-p-chlorophenyl and 2-p-tolyl-N-oxides (301b) and (301d) were also found to react in the same way. The i.r. spectra and ¹H n.m.r. spectra (Table 8) of these products were very similar to those of the imidazole derivative (316a) and are thus assigned the structures (316b-d) by analogy. However, no such addition was found to occur with 2-aryloxazole-3-N-oxides possessing strongly electron-donating or electron-withdrawing substituents in the 2-aryl group even when the reaction mixtures were heated under reflux. This lack of reactivity appears to be independent of the position of the electron-donating or electron-withdrawing substituent. Thus the o-hydroxyphenyl- and p-N,N-dimethylaminophenyl N-oxides (301e) and (301f) failed to react but so also did both the m- and p-nitrophenyl N-oxides (301g) and (301h).

The possible mechanism for the reaction of phenyl isocyanate with the oxazole 3-N-oxides (301) is shown in Scheme 13. This mechanism is also suggested by Goto et al.¹⁸⁷ It is known that oxazoles can be converted into imidazoles because of the masked carbonyl properties of the ring oxygen atom of the oxazole structure. However the recyclisation of the postulated intermediate (328) (see

Scheme 13) is rather unusual. An attempt was made to synthesise this intermediate by treating biacetyl with N-phenylbenzamidine under conditions known to effect the condensation of amidines with carbonyl compounds. However, under the reaction conditions employed no condensation occurred.

The attempted extension of 1,3-dipolar cycloaddition reactions of oxazole 3-N-oxides to other dipolarophiles met with mixed success. 4,5-Dimethyl-2-phenyloxazole 3-N-oxide (301a) reacted readily with *p*-chlorophenyl isocyanate to give a product whose i.r. spectrum and ^1H n.m.r. spectrum (Table 8) were very similar to those of the product (316a) obtained from phenyl isocyanate. This product was also isomeric with that obtained from the N-oxide (301b) and phenyl isocyanate and is thus assigned the structure (325). However 4,5-dimethyl-2-phenyloxazole 3-N-oxide (301a) was recovered unchanged on treatment with methyl isocyanate at room temperature. When the reaction mixture was heated under reflux a gum was obtained which could not be solidified and which was shown by its ^1H n.m.r. spectrum to consist of several components. No attempt was made to separate this mixture. Reaction of the N-oxide (301a) with phenyl isothiocyanate might have been expected to yield the adduct (316a), also, but only a multi-component oil was obtained.

The allylic rearrangement of the adduct (316a) to the hydroxymethyl derivative (322a) was shown to occur also for the adducts (316b-d) and (325) affording the corresponding hydroxymethyl derivatives (322b-d) and (326). This

rearrangement was shown not to be restricted to treatment with aqueous acid. When the imidazole derivative (316a) was warmed in glacial acetic acid in the presence of concentrated sulphuric acid a product was isolated which was identical with that obtained by warming the hydroxymethyl compound (322a) with acetic anhydride. This product is thus formulated as the acetoxymethyl derivative (327a) which presumably arises by attack of acetic acid on the allylic carbonium ion (329) (See Scheme 14). Similarly, heating with methanol in the presence of acid afforded a product with no hydroxyl absorption in its i.r. spectrum and a methyl signal at τ 6.30 in its ^1H n.m.r. spectrum (Figure 41 and Table 9). On the basis of this evidence this product is assigned the structure (327b). Since no reaction occurred on heating the hydroxymethyl derivative (322a) with methanol and concentrated sulphuric acid, formation of the methoxy-derivative (327b) does not arise from the alcohol (322a). This latter control reaction excludes the possibility of rearrangement followed by methylation in the reaction medium. However the corresponding ethyl ether (327c) was not obtained by heating with ethanol and acid. The sole product of this reaction, obtained in low yield, was the hydroxymethylimidazole (322a).

PART THREE

EXPERIMENTAL

NOTES

Infrared spectra were measured for nujol suspensions using a Pye-Unicam SP 200 Spectrophotometer; bands were either strong or very strong, unless otherwise specified (w) as weak or (br) broad.

Nuclear magnetic resonance spectra were measured at 100 MHz using a Varian HA 100 instrument.

Mass spectra were measured at 800 Kv on an A.E.I. MS 902 instrument.

Microanalyses were carried out by Alfred Bernhardt, West Germany and by Mr. Brian Clark, Department of Chemistry, Edinburgh University. Melting points (uncorrected) of all analytical samples were determined on a Kofler-block.

Solvents were of technical grade unless otherwise specified and light petroleum had b.p. 60 - 80°C.

Recovery in chloroform refers to extraction, drying (MgSO_4) and evaporation under reduced pressure.

Alumina was Spence type H.

SECTION ONE

1.1. Preparation of 3-Aminobenzo-1,2,4-triazine
1-N-Oxides (161).

A mixture of the o-nitroaniline derivative (0.072 mol) and cyanamide (20.0g, 0.144 mol) was warmed at 100° giving a melt which was cooled to room temperature, treated with concentrated hydrochloric acid (25.0 ml), and warmed briefly at 100° until a vigorous reaction occurred. After cooling to room temperature the mixture was treated with a solution of sodium hydroxide (20.0g) in water (25.0 ml) and warmed at 100° for 0.5h. The yellow solid which separated on cooling and dilution with water was collected and crystallised from acetic acid to yield the 1-N-oxide (161). (¹H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a).

o-Nitroaniline gave compound (161a), (80%), as a yellow powder, m.p. 275° (lit.,¹²³ 271°) (from acetic acid), ν_{\max} . 3250 and 3100 (NH), 1655 and 1555 cm⁻¹.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 1-N-oxide (161b).

2-Nitro-p-toluidine gave compound (161b), (66%), as yellow platelets, m.p. 279° (lit.,¹¹⁷ 271°) (from acetic acid-water), ν_{\max} . 3350 and 3150 (NH), 1645 and 1550 cm⁻¹.

Found: C, 54.3%; H, 4.6%; N, 31.8%; M⁺, 176
C₈H₈N₄O requires: C, 54.5%; H, 4.5%; N, 31.8%; M, 176.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine 1-N-oxide (161c).

4-Amino-3-nitroanisole gave compound (161c), (91%), as a yellow powder, m.p. 273° (lit.,¹²³ 278-281°) (from acetic acid), ν_{\max} . 3300 and 3100 (NH), 1645 and 1550 cm⁻¹.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine 1-N-oxide (161d).

4-Chloro-2-nitroaniline gave compound (161d), (39%), as a yellow powder, m.p. $309-12^{\circ}$ (lit.,¹¹⁷ $302-5^{\circ}$) (from acetic acid), ν_{\max} . 3350 and 3150 (NH), 1650 and 1560 cm^{-1} .

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 1-N-oxide (161e).

4,5-Dimethyl-2-nitroaniline gave compound (161e), (75%), as a yellow powder, m.p. 288° (decomp.) (from acetic acid), ν_{\max} . 3375 and 3175 (NH), 1645 and 1545 cm^{-1} .

Found: C, 56.3%; H, 5.3%; N, 29.1%; M^+ , 190

$C_9H_{10}N_4O$ requires: C, 56.8%; H, 5.3%; N, 29.5%; M, 190.

1.2. Preparation of 3-Aminobenzo-1,2,4-triazines (162).

The 3-aminobenzo-1,2,4-triazine 1-N-oxide (161) (0.005 mol) was heated under reflux with twice its weight of sodium dithionite (added in two portions, the second portion after one hour) in 70% (v/v) aqueous ethanol (80.0 ml) for 2h. Hot filtration and concentration of the reaction mixture yielded a solid which was washed with water, dried and crystallised from ethanol or acetic acid to give the benzotriazine derivative (162), ν_{\max} . 3300 - 3250 and 3150 - 3125 (NH), 1670 - 1660 and $1560 - 1540\text{ cm}^{-1}$. (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine (162a) was obtained, (65%), as a yellow solid, m.p. 207° (lit.,¹²² 207°) (from ethanol). [Reduction of the N-oxide (161a) with zinc dust and glacial acetic acid¹²⁵ afforded compound (162a) (66%), m.p. 207° (lit.,^{122,125} 207° ; 211.5°).]

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine (162b) was obtained (87%), as a yellow solid, m.p. 227° (lit.,¹¹⁷ 218°) (from

acetic acid-water).

Found: C, 59.8%; H, 4.9%; N, 35.1%; M^+ , 160.
 $C_8H_8N_4$ requires: C, 60.0%; H, 5.0%; N, 35.0%; M, 160.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine (162c) was obtained, (84%), as yellow needles, m.p. 226° (lit.,¹¹⁷ 220°) (from acetic acid-water).

Found: C, 54.4%; H, 4.5%; N, 32.0%.
 $C_8H_8N_4O$ requires: C, 54.5%; H, 4.5%; N, 31.8%.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine (162d) was obtained, (73%), as a yellow solid, m.p. $252-5^\circ$ (lit.,¹¹⁷ 255°) (from acetic acid).

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine (162e) was obtained, (80%), as a yellow solid, m.p. 286° (decomp.) (from acetic acid).

Found: C, 61.5%; H, 5.7%; N, 31.7%; M^+ , 174.
 $C_9H_{10}N_4$ requires: C, 62.1%; H, 5.7%; N, 32.2%; M, 174.

1.3. Preparation of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxides (163).

A suspension of the 3-aminobenzo-1,2,4-triazine 1-N-oxide (161) (0.005 mol) in acetic acid (28 - 180 ml) was stirred and heated at $45-50^\circ$ for 18 - 60h with 30% aqueous hydrogen peroxide (11.5 - 45.0 ml). The suspended solid slowly dissolved giving a clear red solution. The mixture was treated with solid sodium bicarbonate to yield a red solid which was combined with material recovered by extracting the aqueous mother-liquors with chloroform, and crystallised from acetic acid-water to give the pure di-N-oxide (163). (1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a).

Oxidation in acetic acid (32.5 ml) with hydrogen peroxide (11.5 ml) for 18h gave compound (163a) as red plates, (89%), m.p. 219.5° (decomp.) [lit.,¹²⁷ 230° (decomp.)] (from acetic acid), ν_{\max} . 3350, 3200 and 3025 (NH), and 1630cm^{-1} .

Found: C, 46.7%; H, 3.3%; N, 31.8%; M^{+} , 178.

$C_7H_6N_4O_2$ requires: C, 47.2%; H, 3.4%; N, 31.5%; M, 178.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 1,4-di-N-oxide (163b).

Oxidation in acetic acid (36.0 ml) with hydrogen peroxide (13.5 ml) for 18h gave compound (163b) as red needles, (71%), m.p. 220° (decomp.) (from acetic acid-water), ν_{\max} . 3400, 3275 and 3100 (NH), and 1600cm^{-1} .

Found: C, 50.2%; H, 4.2%; N, 29.3%; M^{+} , 192.

$C_8H_8N_4O_2$ requires: C, 50.0%; H, 4.2%; N, 29.2%; M, 192.

(iii) 3-Amino-7-methoxybenzo-1,2,4-triazine 1,4-di-N-oxide (163c).

Oxidation in acetic acid (28.0 ml) with hydrogen peroxide (13.5 ml) for 43h gave compound (163c) as orange needles, (73%), m.p. 225° [lit.,¹²⁷ $213-4^{\circ}$ (decomp.)] (from methanol)] (from acetic acid-water), ν_{\max} . 3425, 3300 and 3200 (NH), and 1620cm^{-1} .

Found: C, 45.3%; H, 3.9%; N, 26.7%.

$C_8H_8N_4O_3$ requires: C, 46.2%; H, 3.8%; N, 26.9%.

(iv) 3-Amino-7-chlorobenzo-1,2,4-triazine 1,4-di-N-oxide (163d).

Oxidation in acetic acid (180 ml) with hydrogen peroxide (45.0 ml) for 18h gave compound (163d) as a red solid, (62%), m.p. 269° (decomp.) [lit.,¹²⁷ 295° (decomp.)] (from acetic acid-water), ν_{\max} . 3400, 3250 and 3025 (NH), and 1600cm^{-1} .

Found: C, 39.3%; H, 2.6%; N, 26.1%.

$C_{7.5}H_{5.4}ClN_4O_2$ requires: C, 39.4%; H, 2.5%; N, 26.3%.

(v) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 1,4-di-N-oxide (163e).

Oxidation in acetic acid (24.0 ml) with hydrogen peroxide (12.0 ml) for 20h, followed by the addition of fresh acetic acid (8.0 ml) and hydrogen peroxide (4.0 ml) and the oxidation continued for a further 40h gave compound (163e) as red needles, (74%), m.p. 242° (decomp.) (from acetic acid-water), ν_{\max} . 3400, 3250 and 3200 (NH), and 1610 cm^{-1} .

Found: C, 51.7%; H, 5.0%; N, 26.7%; M^+ , 206.

$C_{9.5}H_{10.4}N_4O_2$ requires: C, 52.4%; H, 4.9%; N, 27.2%; M, 206.

1.4. Reaction of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxide (163a) with Sodium Dithionite.

The di-N-oxide (163a) heated under reflux with sodium dithionite in 70% (v/v) aqueous ethanol for 20 min, as above, afforded 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a), (50%), m.p. 275° (lit.,¹²⁷ 271°), identical (mixed m.p. and i.r. spectrum) with an authentic sample.

1.5. Reaction of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxides (163) with Acetic Anhydride.

The di-N-oxides (163) were warmed with acetic anhydride for 1 min to give the corresponding monoacetyl derivatives (164), ν_{\max} . 3300-3225 (NH), 1720 (CO) and $1555\text{--}1540\text{ cm}^{-1}$. (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Acetylaminobenzo-1,2,4-triazine 1,4-di-N-oxide (164a) was obtained as yellow needles, (77%), m.p. 190° (from ethanol).

Found: C, 49.2%; H, 3.6%; N, 25.6%; M^+ , 220.

$C_9H_8N_4O_3$ requires: C, 49.1%; H, 3.6%; N, 25.5%; M, 220.

(ii) 3-Acetylamino-7-methylbenzo-1,2,4-triazine 1,4-di-N-oxide (164b) was obtained as an orange solid, (69%), m.p. 212° (from acetic acid-water).

Found: C, 51.3%; H, 4.4%; N, 23.9%; M^+ , 234.

$C_{10}H_{10}N_4O_3$ requires: C, 51.3%; H, 4.3%; N, 23.9%; M, 234.

(iii) 3-Acetylamino-7-methoxybenzo-1,2,4-triazine 1,4-di-N-oxide (164c) was obtained as orange needles, (80%), m.p. 219° (from acetic acid-water).

Found: C, 48.6%; H, 4.0%; N, 22.0%.

$C_{10}H_{10}N_4O_4$ requires: C, 48.0%; H, 4.0%; N, 22.4%.

(iv) 3-Acetylamino-7-chlorobenzo-1,2,4-triazine 1,4-di-N-oxide (164d) was obtained as an orange solid, (77%), m.p. 213° (from acetic acid-water).

Found: C, 42.5%; H, 2.8%; N, 22.1%.

$C_9H_7ClN_4O_3$ requires: C, 42.3%; H, 2.8%; N, 22.0%.

(v) 3-Acetylamino-6,7-dimethylbenzo-1,2,4-triazine 1,4-di-N-oxide (164e) was obtained as a yellow solid, (83%), m.p. 197° (from ethanol).

Found: C, 52.9%; H, 4.8%; N, 22.5%; M^+ , 248.

$C_{11}H_{12}N_4O_3$ requires: C, 53.2%; H, 4.8%; N, 22.6%; M, 248.

1.6. Preparation of 3-Aminobenzo-1,2,4-triazine 2-N-Oxides (165).

(a) A suspension of the 3-aminobenzo-1,2,4-triazine (162a), (162b) or (162e) (0.003 mol) in glacial acetic acid (8-12 ml) was stirred at room temperature for 46h with 30% aqueous

hydrogen peroxide (8.0 ml). The insoluble solid was collected, combined with material obtained by neutralising the filtrate with solid sodium bicarbonate and crystallised from acetic acid to give the corresponding 2-N-oxides, (165a), (165b) or (165e). (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Aminobenzo-1,2,4-triazine 2-N-oxide (165a) was obtained as yellow needles, (46%), m.p. 200° (lit.,¹²⁴ 187°) (from acetic acid-water), ν_{max} . 3400 and 3200-3100 br(NH), and 1680 cm^{-1} .

Found: C, 51.3%; H, 3.6%; N, 34.6%; M^+ , 162.

$\text{C}_7\text{H}_6\text{N}_4\text{O}$ requires: C, 51.8%; H, 3.7%; N, 34.6%; M, 162.

(ii) 3-Amino-7-methylbenzo-1,2,4-triazine 2-N-oxide (165b) was obtained as a yellow solid, (76%), m.p. 203° (from acetic acid-water), ν_{max} . 3400 and 3200-3100 br(NH), and 1680 cm^{-1} .

Found: C, 54.6%; H, 4.5%; N, 31.5%; M^+ , 176.

$\text{C}_8\text{H}_8\text{N}_4\text{O}$ requires: C, 54.5%; H, 4.5%; N, 31.8%; M, 176.

(iii) 3-Amino-6,7-dimethylbenzo-1,2,4-triazine 2-N-oxide (165e) was obtained as a yellow solid, (91%), m.p. 226° (from acetic acid), ν_{max} . 3400 and 3150 (NH), and 1675 cm^{-1} .

Found: C, 57.3%; H, 5.4%; N, 29.6%; M^+ , 190.

$\text{C}_9\text{H}_{10}\text{N}_4\text{O}$ requires: C, 56.8%; H, 5.3%; N, 29.5%; M, 190.

(b) Alternatively the 3-aminobenzo-1,2,4-triazines (162c) or (162d) in glacial acetic acid were treated at room temperature for 80h with 30% aqueous hydrogen peroxide, as in (a) above, and the crude product was crystallised to give the 2-N-oxides (165c) or (165d) (^1H n.m.r. spectra, Table 1, opposite page 39).

(i) 3-Amino-7-methoxybenzo-1,2,4-triazine 2-N-oxide (165c) was obtained as yellow needles, (47%), m.p. 194° [lit.,¹²⁷ 183° (decomp.) (from methanol)] (from acetic acid-water), ν_{\max} . 3400 and 3200-3100 br (NH), and 1680 cm^{-1} .

Found: C, 50.2%; H, 4.4%; N, 29.1%.

$\text{C}_8\text{H}_8\text{N}_4\text{O}_2$ requires: C, 50.0%; H, 4.2%; N, 29.2%.

(ii) 3-Amino-7-chlorobenzo-1,2,4-triazine 2-N-oxide (165d) was obtained as a yellow solid, (74%), m.p. 223° (lit.,¹²⁷ 215°) (from acetic acid-water), ν_{\max} . 3400 and 3100 (NH), and 1680 cm^{-1} .

Found: C, 42.7%; H, 2.6%; N, 28.5%.

$\text{C}_7\text{H}_5\text{ClN}_4\text{O}$ requires: C, 42.7%; H, 2.5%; N, 28.5%.

1.7. Peracid Oxidation of 3-Aminobenzo-1,2,4-triazine (162a) at 50° .

(a) A suspension of 3-aminobenzo-1,2,4-triazine (162a) (0.25g) in glacial acetic acid (6.0 ml) was stirred and heated at $45 - 50^{\circ}$ for 3h with 30% aqueous hydrogen peroxide (2.0 ml). The red solution was neutralised with solid sodium bicarbonate. The precipitate was filtered and combined with material obtained by chloroform extraction of the filtrate, to afford 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a), (70%), identical (m.p. and i.r. spectrum) with an authentic sample.

(b) Repetition of the oxidation described in (a) for 17h afforded a red solution. Dilution with water and neutralisation of the reaction mixture with solid sodium bicarbonate yielded no precipitate. Constant chloroform extraction afforded

3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a), (41%), identical (m.p. and i.r. spectrum) with an authentic sample.

1.8. Peracid Oxidation of 3-Aminobenzo-1,2,4-triazine 2-N-Oxide (165a) at 50°.

A suspension of 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a) (0.2g) in glacial acetic acid (8.0 ml) was stirred and heated at 45 - 50° for 22h with 30% aqueous hydrogen peroxide (3.0 ml). Neutralisation of the red solution with solid sodium bicarbonate afforded no precipitate. Constant chloroform extraction yielded a red gummy solid, which on trituration with ether gave 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a), (36%), identical (m.p. and i.r. spectrum) with an authentic sample.

1.9. Attempted Isomerisation of the 2-N-Oxide (165a) into the 1-N-Oxide (161a) with Perchloric Acid.

A suspension of 3-aminobenzo-1,2,4-triazine 2-N-oxide (165a) (0.1g) in glacial acetic acid (5.0 ml) was treated with perchloric acid (3 drops) and stirred and heated at 45 - 50° for 17h. The yellow solid was filtered and stirred with saturated sodium bicarbonate solution for 30 min. Filtration afforded unchanged starting 2-N-oxide (165a).

1.10. Oxidation of 3-Phenylbenzo-1,2,4-triazine (169).

(a) 3-Phenylbenzo-1,2,4-triazine (169) was prepared by cyclisation¹³⁶ of 1,3,5-triphenylformazan (157; Ar=Ph).¹⁸⁸

(b) 3-Phenylbenzo-1,2,4-triazine 1-N-oxide (170).¹²⁷

(i) A solution of 3-phenylbenzo-1,2,4-triazine (169) (0.5g) in glacial acetic acid (8.0 ml) was stirred and heated at 45 - 50° for 20h with 30% aqueous hydrogen peroxide (3.0 ml). The reaction mixture was cooled affording an orange solid which was combined with material obtained by dilution of the mother liquors with water, giving compound (170), (75%), m.p. 131° (lit.,¹²⁷ 133°), T.L.C. in benzene-ether over silica showed one spot.

(ii) Similarly, oxidation at room temperature for 2 days or 7 days afforded a product in 80% and 85% yield respectively, identical (m.p., mixed m.p., i.r. spectra and T.L.C.) with compound (170). [Robbins and Schofield¹²⁷ obtained 3-phenylbenzo-1,2,4-triazine 2-N-oxide (171) from this treatment, and found that further oxidation at 45 - 50° for 40h converted the 2-N-oxide (171) into 3-phenylbenzo-1,2,4-triazine 1-N-oxide (170).]

1.11. Electrophilic Substitution of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).(a) Nitration of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

Nitration of 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a) by the method of Robbins and Schofield¹²⁷ afforded 3-amino-7-nitrobenzo-1,2,4-triazine 1-N-oxide (172), (84%), m.p. 249° (from glacial acetic acid)[lit.,^{127,134} 289° (decomp.) (from dioxan)], ν_{\max} . 3350 (NH), 1695, 1670 and 1620 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.76 (1 H, d, J 9.0 Hz, H - 8), 1.12 (1 H, dd, J_o 9.0 Hz, J_m 2.25 Hz, H - 6) and 1.95 (1 H, d, J 2.25 Hz, H - 5), M^+ , 207 (M, 207).

(b) Attempted Bromination of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a) (0.65g) was dissolved in glacial acetic acid (80.0 ml) and stirred in an ice-bath. Bromine in glacial acetic acid (0.4 ml of a solution of 10.75g bromine made up to 10.0 ml with glacial acetic acid) was added dropwise giving a red solution. Stirring was continued in the ice-bath for 15 min and then at room temperature for 15 min. Dilution with water afforded the starting N-oxide (161a) (92% recovery).

1.12. Attempted Alkylation of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a) with Methyl Iodide.

3-Aminobenzo-1,2,4-triazine 1-N-oxide (161a) (0.5g) was suspended in acetonitrile (23.0 ml) and stirred in the dark for 20h with methyl iodide (1.0 ml) and then in daylight for a further 7h. Filtration gave the starting N-oxide (161a) (88% recovery).

1.13. Attempted Photochemical Rearrangement of 3-Aminobenzo-1,2,4-triazine 1-N-Oxide (161a).

Irradiation of 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a) (1.5g) in dimethylformamide (200 ml) for 24h afforded the starting N-oxide (161a) (71% recovery).

1.14. Attempted Preparation of 4-Hydroxybenzo-1,2,4-triazine-3(4H)-one 1-N-Oxide (175).

(a) Attempted Diazotisation of 3-Aminobenzo-1,2,4-triazine 1,4-Di-N-oxide (163a).

(i) A solution of 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide

(163a) (0.1g) in 50% (w/v) aqueous sulphuric acid (5.0 ml) was cooled to 0° and treated in portions with solid sodium nitrite (0.06g). The mixture was left at 0° for 5 min then at room temperature for 15 min and poured into water (40 ml). The pH of the solution was adjusted to 6 by the addition of 10% aqueous sodium hydroxide and the reaction mixture was extracted with chloroform. The dried (MgSO_4) chloroform extract was evaporated to afford the starting di-N-oxide (163a) (0.035g, 35%).

(ii) A solution of 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a) (0.1g) in 70% (v/v) aqueous acetic acid (5.0 ml) was cooled to 0° and solid sodium nitrite (0.06g) was added with swirling. The mixture was left at 0° for 5 min, at room temperature for 15 min and then heated under reflux for 1.25h. Evaporation of the acetic acid under reduced pressure afforded the starting di-N-oxide (163a) (0.09g, 90%).

(b) Attempted Oxidation of Benzo-1,2,4-triazin-3(4H)-one 1-N-Oxide (176).

(i) Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176)¹²³ was obtained (78%) by diazotising 3-aminobenzo-1,2,4-triazine 1-N-oxide (161a). It had m.p. 220° (from glacial acetic acid) (lit.,¹²² 219°). [Jiu and Mueller¹²³ report m.p. 242-6° (from methanol)].

(ii) A suspension of benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (0.25g) in glacial acetic acid (7.0 ml) was stirred at 45 - 50° for 19h with 30% aqueous hydrogen peroxide (4.0 ml). Filtration of the mixture afforded the starting N-oxide (176), (0.105g, 42%). No further material was obtained either by

dilution or by neutralisation with solid sodium bicarbonate and extraction with chloroform.

(c) Attempted Oxidation of 3-Chlorobenzo-1,2,4-triazine 1-N-Oxide (177) and 3-Methoxybenzo-1,2,4-triazine 1-N-oxide (178).

(i)(a) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177).

Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) was heated under reflux in excess of phosphorus oxychloride for 2h¹²³ giving 3-chloro-benzo-1,2,4-triazine 1-N-oxide (177) (60%), together with starting material (17%).

(b) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (0.9g) was stirred in glacial acetic acid (25.0 ml) with 30% aqueous hydrogen peroxide (12.0 ml) at 45 - 50° for 48h. The reaction mixture was diluted with water and extracted with chloroform to give unreacted starting N-oxide (0.5g, 55%).

(c) 3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (0.9g) was stirred in glacial acetic acid (25.0 ml) with 30% aqueous hydrogen peroxide (12.0 ml) at 65° for 17h then at 80° for 2h to give a yellow solution. The reaction mixture was cooled, diluted with water and neutralised with solid sodium bicarbonate to give a yellow precipitate (0.84g). The product was washed with chloroform leaving a residue, (0.55g, 67%) identical (m.p. and i.r. spectrum) with benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176). Evaporation of the chloroform washings afforded unreacted starting material (0.29g, 33%).

(ii) (a) 3-Methoxybenzo-1,2,4-triazine 1-N-oxide (178).

3-Chlorobenzo-1,2,4-triazine 1-N-oxide (177) (3.6g) was dissolved in methanol (25.0 ml) with heating. A solution of sodium (0.8g) in methanol (35.0 ml) was added and the reaction mixture was heated under reflux for 1h. The mixture was filtered hot to remove sodium chloride and the filtrate on cooling afforded a pale yellow solid (2.1g). This was combined with material obtained by evaporating the filtrate and washing the residue with water, (0.62g), giving 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178), (2.72g, 77%), as pale yellow needles, m.p. 120° (from methanol), ν_{\max} . 1590 and 1550 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.84 (4H, m, Ar-H) and 5.54 (3H, s, OCH_3).

Found: C, 54.3%; H, 4.0%; N, 23.9%.

$\text{C}_8\text{H}_7\text{N}_3\text{O}_2$ requires: C, 54.2%; H, 4.0%; N, 23.7%.

Acidification of the aqueous washings with dilute hydrochloric acid afforded benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (0.35g, 10%).

(b) A solution of 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178) (0.8g) in glacial acetic acid (15.0 ml) was stirred at $45-50^{\circ}$ for 66h with 30% aqueous hydrogen peroxide (10.0 ml). More hydrogen peroxide (10.0 ml) was added and stirring was continued for a further 6h. The dark yellow solution was diluted with water and neutralised with solid sodium bicarbonate giving the starting N-oxide (178) (0.51g, 64%).

(c) A solution of 3-methoxybenzo-1,2,4-triazine 1-N-oxide (178) (0.8g) in glacial acetic acid (15.0 ml) was stirred at

80° for 24h with 30% aqueous hydrogen peroxide (10.0 ml) giving a dark red solution. On addition of more hydrogen peroxide (10.0 ml) the solution temporarily reverted to yellow with vigorous gas evolution. Stirring was continued for a further 20h and the dark red solution was diluted with water and neutralised with solid sodium bicarbonate. No precipitate was obtained but constant chloroform extraction afforded benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (14%) identical (m.p. and i.r. spectrum) with an authentic sample.

1.15. Attempted Reaction of 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-Oxide (179) with Acetic Anhydride.

(a) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179).

(i) Benzo-1,2,4-triazin-3(4H)-one 1-N-oxide (176) (2.0g) was heated under reflux with anhydrous potassium carbonate (6.0g) in anhydrous acetone (150 ml). Dimethyl sulphate (4.0 ml) was added dropwise and heating was continued for 4h. The reaction mixture was evaporated under reduced pressure and the yellow residue was treated with water. Extraction into chloroform and evaporation of the dried (MgSO_4) extract gave compound (179), (60%), m.p. 229-232° (lit., ¹²³ 235.5 - 240°), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.52 (1H, dd, J_o 8.0 Hz, J_m 2.0 Hz, H - 8), 1.86 (1H, qd, H - 7), 2.22 (1H, dd, H - 5), 2.34 (1H, m, H - 6) and 6.04 (3H, s, N-CH₃), M^+ , 177 (M, 177).

(ii) N-Methyl-o-nitroaniline (2.19g) and cyanamide (1.21g) were fused on a water bath at 100°, then cooled to room temperature and treated with concentrated hydrochloric acid (5.0 ml). The reaction mixture was heated gently then

cooled to room temperature. Sodium hydroxide (4.0 g) in water (5.0 ml) was added and the reaction mixture was heated on a water bath for 0.5h. The orange solid which was obtained on cooling was combined with material obtained by dilution with water to give unreacted N-methyl-o-nitroaniline (recovery quantitative).

(b)(i) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179) (0.53g, 0.003 mol) heated under reflux in acetic anhydride (5.0 ml) for 2h or 7.5h gave the starting N-oxide (179) (recovery 93%) by filtration and evaporation of the reaction mixture.

(ii) 4-Methylbenzo-1,2,4-triazin-3(4H)-one 1-N-oxide (179) (0.53g, 0.003 mol) when heated under reflux with acetic anhydride (5.0 ml) and concentrated sulphuric acid (2 drops) for 0.25h gave a dark green solution. After cooling, filtration and extraction afforded the starting N-oxide (179) (85% recovery).

1.16. Attempted Reaction of 3-Acetylamino-1,2,4-triazine 1,4-Di-N-oxide (164a) with Concentrated Sulphuric Acid.

A solution of 3-acetylamino-1,2,4-triazine 1,4-di-N-oxide (164a) (0.002 mol) in concentrated sulphuric acid (5.0 ml) was stirred at room temperature for 20h. When ether (25.0 ml) was added and the reaction mixture was chilled, a hygroscopic yellow solid was precipitated. Addition of fluoroboric acid to an aqueous solution of the yellow solid failed to give a precipitate. In the presence of a little water the yellow solid was converted into the red 3-aminobenzo-1,2,4-triazine 1,4-di-N-oxide (163a) (25%).

SECTION TWO

2.1. Preparation of Substituted o-Nitroanilines

(i) 4-Bromo-2-nitroaniline (195d)

o-Nitroaniline (27.6g, 0.2 mol) was dissolved in glacial acetic acid (420 ml) and the solution was cooled in ice. A solution of bromine (21.5g, 0.27 mol) made up to 20.0 ml with glacial acetic acid was added dropwise (1.0 - 1.5 ml/min) to the stirred solution. When the addition was complete the reaction mixture was diluted with water and the orange solid which precipitated as needles was filtered off and crystallised from ethanol-water to give 4-bromo-2-nitroaniline (195d) (72%), m.p. 108° (lit.,¹⁵⁷ 111.5°), ν_{\max} . 3450 and 3325 (NH) cm^{-1} .

Using Fuchs,¹⁵⁷ conditions, and adding the bromine solution dropwise or all at once, gave the yellow 4,6-dibromo-2-nitroaniline, m.p. 127° (from ethanol-water), (lit.,¹⁸⁹ 127°), ν_{\max} . 3425 and 3325 (NH) cm^{-1} , τ (CDCl_3) 1.75 (1H, d, J 2.4 Hz, H-3), 2.23 (1H, d, J 2.4 Hz, H-5), and 3.40 (2H, s, NH_2).

(ii) 4,5-Dimethyl-2-nitroaniline (207a).

Nitration¹⁹⁰ of 3,4-dimethylaniline afforded compound (207a) (50%), m.p. 140° (from ethanol) (lit.,¹⁹⁰ 140°), ν_{\max} . 3500 and 3400 (NH), and 1630 (NH) cm^{-1} .

(iii) 4,5-Dimethoxy-2-nitroaniline (207b).

(a) 4,5-Dinitroveratrole obtained (88%) by nitrating¹⁹¹ veratrole had m.p. 122-6° (lit.,¹⁹¹ 131°).

(b) Reduction of 4,5-dinitroveratrole with stannous chloride and ethanolic hydrochloric acid¹⁹² afforded compound (207b)

(75%), m.p. 166° (lit.,¹⁹² 170°), ν_{\max} . 3425 and 3300 (NH) and 1640 (NH) cm^{-1} .

2.2. Preparation of Benzofuroxans (196) and (208).

A series of benzofuroxans (196a-e) and (208a-b) were prepared according to the method of Mallory.¹⁵⁶

Potassium hydroxide (21.0g) and 95% ethanol (250 ml) were heated on a steam bath until solution was obtained. The o-nitroaniline derivative (0.3 mol) was dissolved in the warm ethanolic alkali and the red solution was cooled to 0° , stirred and treated dropwise over 0.5h with a freshly prepared solution of sodium hypochlorite [prepared by passing chlorine gas (41.0g) at 0° into a solution of sodium hydroxide (50.0g) in water (200 ml) containing crushed ice (100g)]. Stirring was continued until the red colour disappeared (1h). The precipitate was collected, washed with water (200 ml), air dried and crystallised to yield the benzofuroxans (196a-e) and (208a-b), ν_{\max} . 1620 and 1590 cm^{-1} .

(i) Benzofuroxan (196a) was obtained in quantitative yield, m.p. 68° (lit.,¹⁵⁶ 73°).

(ii) 5-Methylbenzofuroxan (196b) (91%), had m.p. 95° (lit.,¹⁹³ 98°).

(iii) 5-Methoxybenzofuroxan (196c) (77%), had m.p. 116° (lit.,¹⁹³ 118°).

(iv) 5-Bromobenzofuroxan (196d) (83%), had m.p. 65° (lit.,¹⁹⁴ 69°).

(v) 5-Chlorobenzofuroxan (196e) (90%), had m.p. 48° (lit.,¹⁹⁵ 48°).

(vi) 5,6-Dimethylbenzofuroxan (208a) was obtained in quantitative yield, and had m.p. 137° (lit.,¹⁹⁶ 139°).

(vii) 5,6-Dimethoxybenzofuroxan (208b) formed pink needles (62%), m.p. 221° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 3.04 (1H, s, H-4), 3.26 (1H, s, H-7), and 5.88 (6H, s, OCH_3 -5 and OCH_3 -6).

Found: C, 49.2%; H, 3.9%; N, 14.0%.

$\text{C}_8\text{H}_8\text{N}_2\text{O}_4$ requires: C, 49.0%; H, 4.1%; N, 14.3%.

2.3. Reactions of Benzofuroxans (196) with Active Methylene Compounds.

The benzofuroxan (196) (0.01 mol) and the active methylene compound (0.011 mol) were dissolved in ethanol (20.0 ml) with warming if necessary. Piperidine (1.0 ml) was added and the reaction mixture was stirred at room temperature for 24-72 h to ensure complete reaction. Filtration afforded the quinoxaline 1,4-di-N-oxides (189), (191), (193a) or (206). Working up the mother liquors gave no further product.

(i) 2-Acetyl-3-methylquinoxaline 1,4-di-N-oxide (189a) was obtained from acetylacetone, (50%), m.p. 151° (lit.,¹⁵⁰ 154°), ν_{max} . 1700 (CO) cm^{-1} , τ (CDCl_3) 1.35-1.50 (2H, m, H-5 and H-8), 2.05-2.20 (2H, m, H-6 and H-7), 7.30 (3H, s, COCH_3), and 7.50 (3H, s, CH_3). This product was also obtained (46%) m.p. 152° , by stirring the two reagents in triethylamine (8.0 ml) for 22h. The attempted reaction of benzofuroxan (196a) with acetylacetone using different reaction conditions was unsuccessful. The use of ethereal

hydrogen chloride, or acetic anhydride and solid sodium bicarbonate, as reaction medium, resulted in recovery of starting material (88% and 75% respectively). The use of sodium methoxide yielded a dark, uncharacterised solid.

(ii) 2-Acetyl-3,6-dimethylquinoxaline 1,4-di-N-oxide (206) was obtained from acetylacetone as pale, yellow needles (57%), m.p. 177° (from benzene-light petroleum), T.L.C. over silica in chloroform showed only one spot, ν_{\max} . 1720 (CO) cm^{-1} , τ (CDCl_3) 1.51 (1H, d, J 10.0 Hz, H-8), 1.66 (1H, s, H-5), 2.30 (1H, dd, J_m 2.0 Hz, J_o 10.0 Hz, H-7), 7.30 (3H, s, COCH_3), 7.40 (3H, s, CH_3), and 7.50 (3H, s, CH_3).

Found: C, 62.4%; H, 5.1%; N, 12.1%; M^+ , 232. $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 62.1%; H, 5.2%; N, 12.1%; M, 232.

(iii) 2-Benzoyl-3-methylquinoxaline 1,4-di-N-oxide (189b) was obtained from benzoylacetone as pale yellow needles, (51%), m.p. 211° (from ethanol-acetic acid), T.L.C. over silica in ether showed only one spot, ν_{\max} . 1680 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.10 - 2.44 (9H, m, Ar-H) and 7.19 (3H, s, CH_3).

Found: C, 68.9%; H, 4.4%; N, 9.5%. $\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 68.6%; H, 4.3%; N, 10.0%.

(iv) 3-Amino-2-cyanoquinoxaline 1,4-di-N-oxide (191a) was obtained from malononitrile, (82%), m.p. 238° (decomp.) [lit., 151 232° (decomp.)], ν_{\max} . 3375 and 3275 (NH), 2200 (CN), and 1630 cm^{-1} .

(v) 2-Cyano-4-hydroxyquinoxalin-3(4H)-one 1-N-oxide (193a).

Reaction of benzofuroxan (52; R=H) and ethyl cyanoacetate, as above, afforded a red solid in very poor yield (19%). Because of the similarity of its i.r. spectrum to that of the

ammonium salt obtained below, this red solid is assumed to be the piperidine salt of the N-oxide (193a).

Because of the very low yield, a different procedure was required to synthesise compound (193a).

The ethanol solution of the two reagents was saturated with ammonia gas and left stoppered at room temperature for 24h. The precipitated, red ammonium salt was dissolved in water and filtered to remove insoluble impurity. Acidification of the filtrate with glacial acetic acid afforded a by-product, $C_9H_7N_3O_4$, (14%), which was not characterised.

Found: C, 49.0%; H, 3.6%; N, 16.9%.

$C_9H_7N_3O_4$ requires: C, 48.9%; H, 3.2%; N, 19.0%.

The mother-liquors were evaporated under reduced pressure to give a red solid, which was triturated with dilute sulphuric acid to afford 2-cyano-4-hydroxyquinoxalin-3(4H)-one 1-N-oxide (193a), (24%), as yellow needles, m.p. 235° (from methanol), ν_{\max} . 3400 br(OH) and 1620 (CO) cm^{-1} , τ (CF_3CO_2H) 1.52 (1H, d, J 8.0 Hz, H-8), and 1.86-2.36 (3H, m, Ar-H).

Found: C, 53.1%; H, 2.7%; N, 20.9%; M^+ , 203.

$C_9H_5N_3O_3$ requires: C, 53.2%; H, 2.5%; N, 20.7%; M, 203.

2.4. Attempted Reaction of 2-Acetyl-3-methylquinoxaline 1,4-Di-N-oxide (189a) with Peracetic Acid.

(i) A solution of 2-acetyl-3-methylquinoxaline 1,4-di-N-oxide (189a) (0.22g) in glacial acetic acid (4.0 ml) was treated with 30% (v/v) aqueous hydrogen peroxide (1.0 ml) and the reaction mixture was stirred at room temperature for 17h.

The reaction mixture was diluted with water and concentrated under reduced pressure. Neutralisation with solid sodium bicarbonate, followed by chloroform extraction, afforded the starting N-oxide (0.15g, 68% recovery).

(ii) Heating under reflux for 17h caused decomposition and only a dark, intractable gum was obtained.

2.5. Preparation of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199) and (209).

Benzoylacetonitrile was prepared by the method of Gabriel and Eschenbach,¹⁹⁷ (quantitative yield), m.p. 79° (lit.,¹⁹⁷ 81°). The benzofuroxan (196) or (208) (0.1 mol) and benzoylacetonitrile (0.11 mol) were suspended in ethanol (450-750 ml) and the reaction mixture was saturated with ammonia gas. The resulting red solution, or suspension, was left stoppered at room temperature for 20h. The yellow solid which precipitated was collected and combined with material obtained by concentrating the mother-liquors and crystallised to give the pure di-N-oxide (199) or (209), ν_{\max} . 2250 (CN) and 1600 cm^{-1} , ^1H n.m.r. spectra, Table 4.

(i) 3-Cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) was obtained as yellow needles, (74%), m.p. 208° (from acetic acid-water).

Found: C, 68.2%; H, 3.6%; N, 16.2%.

$\text{C}_{15}\text{H}_9\text{N}_3\text{O}_2$ requires: C, 68.4%; H, 3.5%; N, 16.0%.

This product was also obtained by stirring the two reagents for 20h in (a) triethylamine (15.0 ml) (45% yield),
(b) dimethylformamide (6.0 ml) and piperidine (1.0 ml)

(71% yield), or (c) ethanol (20.0 ml) and piperidine (1.0 ml) (73% yield).

(ii) 3-Cyano-6-methyl-2-phenylquinoxaline 1,4-di-N-oxide (199b) was obtained as yellow plates, (62%; 91%, based on recovered starting material, isolated from the mother liquors), m.p. 211.5° (from acetic acid-water).

Found: C, 69.3%; H, 4.2%; N, 15.0%.

$C_{16}H_{11}N_3O_2$ requires: C, 69.3%; H, 4.0%; N, 15.2%.

(iii) 3-Cyano-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (199c) was obtained as yellow needles, (74%), m.p. 223° (from acetic acid-water).

Found: C, 65.8%; H, 4.1%; N, 14.2%.

$C_{16}H_{11}N_3O_3$ requires: C, 65.5%; H, 3.8%; N, 14.3%.

(iv) 6-Bromo-3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199d) was obtained as yellow needles, (60%), m.p. 216° (from acetic acid-water).

Found: C, 52.2%; H, 2.3%; N, 12.0%.

$C_{15}H_8BrN_3O_2$ requires: C, 52.6%; H, 2.3%; N, 12.3%.

(v) 6-Chloro-3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199e) was obtained as yellow plates, (75%), m.p. 218° (from glacial acetic acid).

Found: C, 60.4%; H, 2.7%; N, 14.2%.

$C_{15}H_8ClN_3O_2$ requires: C, 60.5%; H, 2.7%; N, 14.1%.

(vi) 3-Cyano-6,7-dimethylquinoxaline 1,4-di-N-oxide (209a) was obtained as yellow plates, (67%), m.p. 224° (from glacial acetic acid).

Found: C, 70.0%; H, 4.4%; N, 14.1%.

$C_{17}H_{13}N_3O_2$ requires: C, 70.1%; H, 4.5%; N, 14.4%.

(vii) 3-Cyano-6,7-dimethoxyquinoxaline 1,4-di-N-oxide (209b) prepared as above, was contaminated with 5,6-dimethoxybenzofuroxan (208b) and the two compounds could not be separated by crystallisation. A modified procedure was therefore used. A suspension of 5,6-dimethoxybenzofuroxan (0.1 mol) and benzoylacetonitrile (0.11 mol) in dimethylformamide (30.0 ml) was treated with piperidine (1.0 ml). The reaction mixture was stirred at room temperature for 2h and more piperidine (1.0 ml) was added. After stirring for 24h the yellow solid was collected to give compound (209b), (83%), as tiny, yellow needles, m.p. 277° (from acetic acid-water).

Found: C, 63.8%; H, 4.0%; N, 13.1%.

$C_{17}H_{13}N_3O_4$ requires: C, 63.2%; H, 4.1%; N, 13.0%.

2.6. Attempted Reaction of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxide (199a) with Nucleophiles.

A suspension of 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.001 mol) in ethanol (6.0 ml) was heated under reflux with (a) aniline (0.001 mol), and (b) ethyl cyanoacetate (0.001 mol), for 2h. The yellow solid obtained by hot filtration was combined with the precipitate which separated on cooling. A further, small amount of material was obtained by evaporating the mother-liquors under reduced pressure and triturating the residual gum with ether-light petroleum. The combined fractions afforded the starting N-oxide (88-92% recovery).

2.7. Reaction of the 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199) and (209a) with Sodium Ethoxide.

The 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199) or (209a) (0.02 mol) was heated under reflux for 2h with a solution of sodium (0.03g atom) in dry ethanol (100 ml). Evaporation of the reaction mixture under reduced pressure gave a yellow solid which was washed with water and filtered to afford [except in (iii) - see below] unreacted starting material. Acidification of the filtrate with 2N aqueous hydrochloric acid gave a pale yellow solid which was collected and dried to afford the corresponding 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202) or (210a), ^1H n.m.r. spectra, Table 4.

(i) 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) was obtained as pale yellow prisms, (67%; 74% based on recovered starting material), m.p. 196° (from benzene-light petroleum), ν_{max} . 2800-2600 br(OH) , and 1610 cm^{-1} .

Found: C, 65.9%; H, 4.0%; N, 11.1%.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_3$ requires: C, 66.1%; H, 4.0%; N, 11.0%.

Earlier attempts had been made to obtain this compound as follows:-

(a) A solution of 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.001 mol) in glacial acetic acid (5.0 ml) was treated with 20% (w/v) aqueous sulphuric acid and heated under reflux for 3h. The reaction mixture was concentrated and filtered, and the residue was well washed with water, to afford the starting di-N-oxide (88% recovery).

(b) 3-Cyano-2-phenylquinoxaline 1,4-di-N-oxide (199a) (0.01 mol) was heated under reflux in 10% aqueous sodium hydroxide

(80.0 ml) for 1h. Hot filtration and acidification of the filtrate to pH 7 with 2N aqueous hydrochloric acid afforded 3-carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201a) (21%), identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained as described below. Further acidification to pH 1 with 2N aqueous hydrochloric acid (acidification with dilute sulphuric acid complicated the work-up because of the formation of a stable salt) afforded 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) (72%), identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained as described above.

(ii) 4-Hydroxy-6-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202b) was obtained as yellow needles (76%; quantitative yield based on recovered starting material), m.p. 218° (from benzene-light petroleum), ν_{\max} . 2700-2600 br (OH), and 1605 (CO) cm^{-1} .

Found: C, 67.2%; H, 4.5%; N, 10.3%.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 67.2%; H, 4.5%; N, 10.4%.

(iii) 4-Hydroxy-6-methoxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202c) was obtained as pale yellow needles (76%), m.p. 243° (from benzene-light petroleum), ν_{\max} . 2750-2600 br (OH), 1670 (CO) and 1605 cm^{-1} .

Found: C, 63.6%; H, 4.1%; N, 9.5%.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_4$ requires: C, 63.4%; H, 4.3%; N, 9.9%.

This product was accompanied by an initially insoluble residue (see above) which proved to be 3-carbamoyl-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (201c) (15%), identical

(m.p., mixed m.p. and i.r. spectrum) with an authentic sample prepared as described below.

(iv) 6-Bromo-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202d) was obtained as yellow platelets, (80%; 99% based on recovered starting material), m.p. 231° (from benzene), ν_{\max} . 2700-2400 br (OH), 1650 (CO) and 1600 cm^{-1} .

Found: C, 50.8%; H, 2.8%; N, 9.0%.

$C_{14}H_9BrN_2O_3$ requires: C, 50.5%; H, 2.7%; N, 8.4%.

(v) 6-Chloro-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202e) was obtained as pale yellow needles, (75%), m.p. 228° (from benzene), ν_{\max} . 2700-2600 br (OH), and 1610-1600 br (CO) cm^{-1} .

Found: C, 58.3%; H, 2.8%; N, 9.8%.

$C_{14}H_9ClN_2O_3$ requires: C, 58.2%; H, 3.1%; N, 9.7%.

(vi) 6,7-Dimethyl-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (210a) was obtained as yellow needles, (70%; 91% based on recovered starting material), m.p. 225° (from benzene-ethanol), ν_{\max} . 2700-2650 br (w)(OH), and 1605 (CO) cm^{-1} .

Found: C, 67.5%; H, 4.7%; N, 9.5%.

$C_{16}H_{14}N_2O_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

2.8. Acid Hydrolysis of 3-Cyano-2-phenylquinoxaline 1,4-Di-N-oxides (199).

The 3-cyano-2-phenylquinoxaline 1,4-di-N-oxide (199) (0.005 mol) was treated with concentrated sulphuric acid (5.0 ml) and water (0.2 ml) giving a red solution. The reaction mixture was heated on a water bath at 60° for 5h

and then poured onto ice (7.5g). The pale yellow solid thus obtained was filtered off, washed well with water and crystallised from acetic acid-water to yield the 3-carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201), ν_{\max} . 3375 and 3175 (NH), and 1680 (CO) cm^{-1} .

(i) 3-Carbamoyl-2-phenylquinoxaline 1,4-di-N-oxide (201a) was obtained as pale yellow needles, (82%), m.p. 270° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.22 (2H, m, Ar-H), 1.80 (2H, m, Ar-H), and 2.34 (5H, s, Ar-H).

Found: C, 64.2%; H, 3.9%; N, 15.1%; M^+ , 281.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_3$ requires: C, 64.1%; H, 3.9%; N, 14.9%; M, 281.

(ii) 3-Carbamoyl-6-methoxy-2-phenylquinoxaline 1,4-di-N-oxide (201c) was obtained as pale yellow needles, (81%), m.p. 259° (from acetic acid-water), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.33 (1H, d, J 9.5 Hz, H-8), 1.96 (1H, d, J 2.5 Hz, H-5), 2.17 (1H, dd, J_m 2.5 Hz, J_o 9.5 Hz, H-7), 2.37 (5H, s, Ar-H), and 5.85 (3H, s, OCH_3).

Found: C, 62.1%; H, 4.3%; N, 13.9%.

$\text{C}_{16}\text{H}_{13}\text{N}_3\text{O}_4$ requires: C, 61.7%; H, 4.2%; N, 13.5%.

2.9. Preparation of 2-Nitro- α -phenylacetanilides (214) and (219).

The 2-nitro- α -phenylacetanilides (214) and (219) were prepared according to the method of Tennant.¹⁴⁸

The α -nitroaniline derivative (195) or (207) (0.1 mol) was heated with phenylacetyl chloride (13.4 ml, 0.1 mol) in dry benzene (50.0 ml) on a boiling water bath for 2h. Removal of the solvent under reduced pressure gave a gum which crystallised on rubbing to give the corresponding 2-nitro- α -phenylacetanilide (214) or (219).

(i) 2-Nitro- α -phenylacetanilide (214a) (71%), had m.p. 79° (lit., $^{148} 84^{\circ}$), ν_{\max} . 3325 (NH), 1690 (CO) and 1580 cm^{-1} .

(ii) 4-Methyl-2-nitro- α -phenylacetanilide (214b) was obtained as pale yellow needles in quantitative yield, m.p. 94° (from benzene-light petroleum), ν_{\max} . 3300 and 3250 (NH), 1700 and 1670 (CO), 1580, and 1520 and 1340 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.65 (1H, d, J 8.75 Hz, H-6), 1.97 (1H, d, J 1.5 Hz, H-3), 2.43 (1H, dd, J_o 8.75 Hz, J_m 1.5 Hz, H-5), 2.58 (5H, m, Ar-H), 5.98 (2H, s, CH_2), and 7.56 (3H, s, CH_3).

Found: C, 66.9%; H, 5.1%; N, 10.4%.

$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 66.7%; H, 5.2%; N, 10.4%.

(iii) 4-Methoxy-2-nitro- α -phenylacetanilide (214c) (98%), had m.p. 84° (lit., $^{149} 84^{\circ}$), ν_{\max} . 3300 (NH), 1660 (CO), 1580, and 1520 and 1350 (NO_2) cm^{-1} .

(iv) 4-Bromo-2-nitro- α -phenylacetanilide (214d) was obtained as yellow needles in quantitative yield, m.p. 124° (from benzene-light petroleum), ν_{\max} . 3350 (NH), 1685 (CO), 1580, and 1500 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.52 (1H, d, J 9.0 Hz, H-6), 1.70 (1H, d, J 2.25 Hz, H-3), 2.18 (1H, dd, J_o 9.0 Hz, J_m 2.25 Hz, H-5), 2.60 (5H, m, Ar-H), and 6.00 (2H, s, CH_2).

Found: C, 50.6%; H, 3.3%; N, 8.6%.

$\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}_3$ requires: C, 50.1%; H, 3.3%; N, 8.4%.

(v) 4-Chloro-2-nitro- α -phenylacetanilide (214e) (70%), had m.p. 103° (lit., $^{149} 110^{\circ}$), ν_{\max} . 3300 (NH), 1680 (CO), 1580, and 1520 and 1360 (NO_2) cm^{-1} .

(vi) 4,5-Dimethyl-2-nitro- α -phenylacetanilide (219a) was obtained as pale yellow needles, (87%), m.p. 170° (from benzene), ν_{\max} . 3300 (NH), 1675 (CO), 1580, and 1540 and 1360 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.75 (1H, s, H-3), 2.03 (1H, s, H-6), 2.57 (5H, s, Ar-H), 6.00 (2H, s, CH_2), 7.61 (3H, s, CH_3), and 7.68 (3H, s, CH_3).

Found: C, 68.0%; H, 5.4%; N, 9.7%.

$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3$ requires: C, 67.6%; H, 5.7%; N, 9.9%.

(vii) 4,5-Dimethoxy-2-nitro- α -phenylacetanilide (219b) was obtained as yellow needles, (66%), m.p. 151° (from benzene-light petroleum), ν_{\max} . 3275 (NH), 1675 (CO), 1585, and 1520 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.59 (1H, s, H-3), 2.20 (1H, s, H-6), 2.58 (5H, m, Ar-H), 5.94 (3H, s, OCH_3), 5.98 (2H, s, CH_2), and 6.01 (3H, s, OCH_3).

Found: C, 60.6%; H, 5.0%; N, 8.6%.

$\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_5$ requires: C, 60.8%, H, 5.1%; N, 8.9%.

(viii) 2,4-Dinitro- α -phenylacetanilide (214f) was obtained as pale yellow needles (70%; 98% based on recovered starting material, obtained by hot filtration of the reaction mixture), m.p. 112° (from benzene-light petroleum), ν_{\max} . 3325 (NH), 1710 (CO), 1600, and 1520 and 1350 (NO_2) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.98 (1H, d, J 9.0 Hz, H-3), 1.03 (1H, d, J 2.5 Hz, H-6), 1.50 (1H, dd, J_m 2.5 Hz, J_o 9.0 Hz, H-5), 2.58 (3H, m, Ar-H), 2.76 (2H, m, Ar-H) and 5.97 (2H, s, CH_2).

Found: C, 55.0%; H, 3.7%; N, 13.7%.

$\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_5$ requires: C, 55.8%; H, 3.7%; N, 14.0%.

2.10. Preparation of 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides (215) and (220a).

A series of 2-phenylquinoxalin-3(4H)-one 1-N-oxides (215) and (220a) was prepared according to the method of Ahmad.¹⁴⁹

The 2-nitro- α -phenylacetanilide derivative (214) or (219) (0.02 mol) was dissolved in a mixture of pyridine (25.0 ml) and 20% aqueous potassium hydroxide (25.0 ml) and the mixture was heated on a boiling water bath for 1h with vigorous stirring. The reaction mixture was diluted with water and the precipitated *o*-nitroaniline derivative (formed by competing hydrolysis of the 2-nitro- α -phenylacetanilide) was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and the yellow solid was collected and washed with water to afford the corresponding 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215) or (220a), ¹H n.m.r. spectra, Table 3.

(i) 2-Phenylquinoxalin-3(4H)-one 1-N-oxide (215a) (60%), had m.p. 282-6° (lit.,^{148,149} 285°; 307°), ν_{\max} . 1650 (CO) and 1620 cm^{-1} .

(ii) 7-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215b) was obtained as pale yellow needles, (34%), m.p. 296° (from acetic acid-water), ν_{\max} . 3150 (NH) and 1640 (CO) cm^{-1} .

Found: C, 71.3%; H, 4.6%; N, 11.0%.

C₁₅H₁₂N₂O₂ requires: C, 71.4%; H, 4.8%; N, 11.1%.

4-Methyl-2-nitroaniline (195b) (28%) was obtained as by-product, identical (m.p. and i.r. spectrum) with an authentic sample.

(iii) 7-Methoxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215c) (66%), had m.p. 287° (lit.,¹⁴⁹ $297-300^{\circ}$), ν_{\max} . 1650 (CO) and 1600 cm^{-1} .

(iv) 7-Bromo-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215d) was obtained as yellow platelets, (56%), m.p. 298° (from acetic acid-water), ν_{\max} . 1660 (CO) and 1620 cm^{-1} .

Found: C, 53.1%; H, 2.8%; N, 8.8%.

$\text{C}_{14}\text{H}_9\text{BrN}_2\text{O}_2$ requires: C, 53.0%; H, 2.8%; N, 8.8%.

(v) 7-Chloro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215e) (67%), had m.p. 286° [lit.,¹⁴⁹ 313° (decomp.)], ν_{\max} . 1650 (CO) and 1620 cm^{-1} .

(vi) 6,7-Dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (220a) was obtained as yellow needles, (43%), m.p. 286° (from acetic acid-water), ν_{\max} . 1660 (CO) and 1630 cm^{-1} .

Found: C, 72.2%; H, 4.9%; N, 10.0%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

4,5-Dimethyl-2-nitroaniline (207a) (48%), was obtained as by-product, m.p. 139° (lit.,¹⁹⁰ 140°).

(vii) Attempted cyclisation of 4,5-dimethoxy-2-nitro- α -phenyl-acetanilide (219b) afforded 4,5-Dimethoxy-2-nitroaniline (207b) (76%) as the sole product, m.p. 170° (lit.,¹⁹² 170°).

(viii) 7-Nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) was obtained as buff platelets, (55%), m.p. 276° (from glacial acetic acid), ν_{\max} . 1680 (CO) and 1620 cm^{-1} .

Found: C, 59.3%; H, 3.1%; N, 14.8%.

$\text{C}_{14}\text{H}_9\text{N}_3\text{O}_4$ requires: C, 59.4%; H, 3.2%; N, 14.8%.

2,4-Dinitroaniline (19%) was obtained as by-product, identical with an authentic sample.

2.11. Preparation of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (216) and (220b).

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215) or (220a) (1.0g) was dissolved in 10% aqueous sodium hydroxide (10.0 ml) and dimethyl sulphate (2.5 ml) was added dropwise with vigorous shaking, always keeping the solution alkaline. The reaction mixture was heated on a boiling water bath for 15 min and the yellow solid which separated on cooling was collected, dried and crystallised to afford the corresponding N-methyl derivative (216) or (220b), ^1H n.m.r. spectra, Table 3.

(i) 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) was obtained in quantitative yield, identical (m.p. and i.r. spectrum) with an authentic sample.¹⁴⁸

(ii) 4,7-Dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216b) was obtained as pale yellow needles, (77%), m.p. 238° (from acetic acid-water), $\nu_{\text{max.}}$ 1630 (CO) and 1590 cm^{-1} .

Found: C, 72.1%; H, 5.4%; N, 10.4%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

(iii) 7-Methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216c) was obtained as orange cubes in quantitative yield, m.p. 279° (from acetic acid-ethanol), $\nu_{\text{max.}}$ 1630 cm^{-1} .

Found: C, 68.0%; H, 4.9%; N, 9.4%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

(iv) 7-Bromo-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216d) was obtained as pale yellow needles, (77%), m.p. 219° (from acetic acid-water), ν_{\max} . 1635 (CO) and 1610 cm^{-1} .

Found: C, 54.3%; H, 3.2%; N, 8.5%.

$C_{15}H_{11}BrN_2O_2$ requires: C, 54.4%; H, 3.3%; N, 8.5%.

(v) 7-Chloro-4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216e) was obtained as pale yellow needles, (90%), m.p. 190° (from acetic acid-water), ν_{\max} . 1640 (CO) and 1580 cm^{-1} .

Found: C, 62.4%; H, 5.7%; N, 9.8%.

$C_{15}H_{11}ClN_2O_2$ requires: C, 62.8%; H, 5.8%; N, 10.0%.

(vi) 2-Phenyl-4,6,7-trimethylquinoxalin-3(4H)-one 1-N-oxide (220b) was obtained as yellow needles, (92%), m.p. 200° (from acetic acid-water), ν_{\max} . 1630 (CO) and 1620 cm^{-1} .

Found: C, 73.4%; H, 5.7%; N, 9.8%.

$C_{17}H_{16}N_2O_2$ requires: C, 72.8%; H, 5.8%; N, 10.0%.

(vii) 4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216f).

The above method only succeeded in forming the sodium salt of the starting material (215f), even when the reaction mixture was shaken for 12h.

7-Nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) (0.5 g) was heated under reflux in anhydrous acetone (50.0 ml) with anhydrous potassium carbonate (1.5 g). Dimethyl sulphate (1.0 ml) was added dropwise and heating was continued for 4h. The reaction mixture was evaporated under reduced pressure and the residue was treated with water giving a yellow gummy solid which was extracted into chloroform. Evaporation of

the extract gave the compound (216f) as yellow needles, (79%), m.p. 208° (from ethanol-acetic acid), ν_{\max} . 1660 (CO), 1610, and 1535 and 1350 (NO_2) cm^{-1} .

Found: C, 60.7%; H, 3.6%; N, 14.2%.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{O}_4$ requires: C, 60.6%; H, 3.7%; N, 14.1%.

2.12. Preparation of 2-Phenylquinoxalin-3(4H)-ones (204), (211), (217) and (218).

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (202), (210a), (215), (216) or (220) (0.5 g) was heated under reflux with twice its weight of sodium dithionite (added in two portions, the second portion after 1h) in 70% v/v aqueous ethanol (10.0 - 50.0 ml) for 2h. Filtration and concentration of the reaction mixture yielded a solid which was washed with water, dried and crystallised from ethanol or acetic acid to give the corresponding 2-phenylquinoxalin-3(4H)-one derivative (204), (211a) or (217), ν_{\max} . 1660 (CO) cm^{-1} , or (211b) or (218), ν_{\max} . 1640 (CO) cm^{-1} , ^1H n.m.r. spectra, Table 3.

(i) 2-Phenylquinoxalin-3(4H)-one (204a).

(a) Reduction of compound (215a) afforded compound (204a), (81%), m.p. 253° (lit.,¹⁴⁹ 260°).

(b) Reduction of compound (202a) afforded compound (204a), (69%), m.p. 256° , identical (mixed m.p. and i.r. spectrum) with an authentic sample.¹⁴⁹

(ii) 4-Methyl-2-phenylquinoxalin-3(4H)-one (218a) was obtained by reducing compound (216a), (90%), m.p. 135° (lit.,¹⁴⁹ 138°).

(iii) 6-Methyl-2-phenylquinoxalin-3(4H)-one (204b) was obtained by reducing compound (202b), as pale yellow needles, (83%),

m.p. 237° (from ethanol-water).

Found: C, 76.5%; H, 5.0%; N, 11.9%.

C₁₅H₁₂N₂O requires: C, 76.3%; H, 5.1%; N, 11.9%.

(iv) 7-Methyl-2-phenylquinoxalin-3(4H)-one (217b) was obtained by reducing compound (215b), as pale yellow needles, in quantitative yield, m.p. 248° (from ethanol).

Found: C, 76.2%; H, 5.1%; N, 11.7%.

C₁₅H₁₂N₂O requires: C, 76.3%; H, 5.1%; N, 11.9%.

(v) 4,7-Dimethyl-2-phenylquinoxalin-3(4H)-one (218b) was obtained by reducing compound (216b), as pale yellow needles, (85%), m.p. 144° (from ethanol).

Found: C, 77.4%; H, 5.5%; N, 10.6%.

C₁₆H₁₄N₂O requires: C, 76.8%; H, 5.6%; N, 11.2%.

(vi) 6-Methoxy-2-phenylquinoxalin-3(4H)-one (204c) was obtained by reducing compound (202c), as cream needles, in quantitative yield, m.p. 239° (from acetic acid-water).

Found: C, 70.8%; H, 4.8%; N, 11.4%.

C₁₅H₁₂N₂O₂ requires: C, 71.4%; H, 4.8%; N, 11.1%.

(vii) 7-Methoxy-2-phenylquinoxalin-3(4H)-one (217c) was obtained by reducing compound (215c), as small yellow needles, in quantitative yield, m.p. 249° (lit., ¹⁴⁹ 235°) (from acetic acid-water).

Found: C, 71.3%; H, 4.5%; N, 10.7%.

Calc. for C₁₅H₁₂N₂O₂: C, 71.4%; H, 4.8%; N, 11.1%.

(viii) 7-Methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (218c) was obtained by reducing compound (216c), as a yellow solid,

(82%), m.p. 165.5° (from acetic acid-ethanol).

Found: C, 72.3%; H, 5.4%; N, 10.7%.

$C_{16}H_{14}N_2O_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

(ix) 6-Bromo-2-phenylquinoxalin-3(4H)-one (204d) was obtained by reducing compound (202d), as yellow needles, (94%), m.p. 287° (from acetic acid-ethanol).

Found: C, 55.3%; H, 3.1%; N, 9.0%.

$C_{14}H_9BrN_2O$ requires: C, 55.8%; H, 3.0%; N, 9.3%.

(x) 7-Bromo-2-phenylquinoxalin-3(4H)-one (217d) was obtained by reducing compound (215d), as pale yellow needles, (74%), m.p. 298° (from acetic acid-water).

Found: C, 55.7%; H, 2.9%; N, 9.1%.

$C_{14}H_9BrN_2O$ requires: C, 55.8%; H, 3.0%; N, 9.3%.

(xi) 7-Bromo-4-methyl-2-phenylquinoxalin-3(4H)-one (218d) was obtained by reducing compound (216d), as pale yellow needles, (76%), m.p. 173.5° (from acetic acid-ethanol).

Found: C, 57.5%; H, 3.5%; N, 9.2%.

$C_{15}H_{11}BrN_2O$ requires: C, 57.1%; H, 3.5%; N, 8.9%.

(xii) 6-Chloro-2-phenylquinoxalin-3(4H)-one (204e) was obtained by reducing compound (202e), as pale yellow needles, (93%), m.p. 265.5° (from acetic acid-water) (lit.,¹³⁸ 275°)

Found: C, 65.8%; H, 3.4%; N, 10.9%.

Calc. for $C_{14}H_9ClN_2O$: C, 65.5%; H, 3.5%; N, 10.9%.

(xiii) 7-Chloro-2-phenylquinoxalin-3(4H)-one (217e) was obtained by reducing compound (215e), in quantitative yield, m.p. 258° (lit.,¹⁴⁹ 263°).

(v) 4-Acetoxy-6-chloro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (203e) was obtained as pale yellow needles, (73%), m.p. 167° (from ethanol-water).

Found: C, 58.4%; H, 3.7%; N, 8.1%.

C₁₆H₁₁ClN₂O₄ requires: C, 58.1%; H, 3.3%; N, 8.5%.

(vi) 4-Acetoxy-6,7-dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (210b) was obtained as cream needles, (90%), m.p. 170° (from ethanol).

Found: C, 66.7%; H, 5.1%; N, 8.8%.

C₁₈H₁₆N₂O₄ requires: C, 66.7%; H, 5.0%; N, 8.6%.

(b) Prolonged treatment

The 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202) or (210a) (0.5 g) was heated under reflux in acetic anhydride (2.5 ml) for 4.5h. The reaction mixture was evaporated under reduced pressure and the residue triturated with ether giving a solid which was combined with material obtained by treating the re-evaporated mother-liquors with water, and crystallised to give the products (221a), (222), (223) or (224a), ¹H n.m.r. spectra, Table 6.

(i) 4,6-Diacetoxy-2-phenylquinoxalin-3(4H)-one (221a) was obtained as white needles, (80%), m.p. 158.5° (from ethanol), ν_{\max} . 1790, 1740 and 1670 (CO) cm⁻¹.

Found: C, 63.9%; H, 4.5%; N, 8.4%.

C₁₈H₁₄N₂O₅ requires: C, 63.9%; H, 4.2%; N, 8.3%.

(ii) 4-Acetoxy-6-acetoxymethyl-2-phenylquinoxalin-3(4H)-one (223) was obtained as a tan solid, (66%), m.p. 114° (from ethanol), ν_{\max} . 1800, 1730 and 1670 (CO), and 1620 cm⁻¹.

Found: C, 64.6%; H, 4.4%; N, 8.4%.

C₁₉H₁₆N₂O₅ requires: C, 64.8%; H, 4.6%; N, 8.0%.

(iii) 4,8-Diacetoxy-6-methoxy-2-phenylquinoxalin-3(4H)-one (222b) was obtained as cream needles, (52%), m.p. 158° (from ethanol), ν_{\max} . 1800, 1760 and 1680 (CO) and 1630 cm⁻¹.

Found: C, 62.6%; H, 4.5%; N, 7.5%.

C₁₉H₁₆N₂O₆ requires: C, 62.0%; H, 4.4%; N, 7.6%.

(iv) 6-Bromo-4,8-diacetoxy-2-phenylquinoxalin-3(4H)-one (222c) was obtained as cream needles, (57%), m.p. 193° (from ethanol), ν_{\max} . 1790, 1760 and 1685 (CO) cm⁻¹.

Found: C, 52.3%; H, 3.1%; N, 6.7%.

C₁₈H₁₃BrN₂O₅ requires: C, 51.8%; H, 3.1%; N, 6.7%.

(v) 6-Chloro-4,8-diacetoxy-2-phenylquinoxalin-3(4H)-one (222d) was obtained as cream needles, (48%), m.p. 187° (from ethanol-acetic acid), ν_{\max} . 1800, 1775, and 1690 (CO), and 1610 cm⁻¹.

Found: C, 58.0%; H, 3.6%; N, 7.7%.

C₁₈H₁₃ClN₂O₅ requires: C, 58.1%; H, 3.5%; N, 7.6%.

(vi) 4-Acetoxy-6-acetoxymethyl-7-methyl-2-phenylquinoxalin-3(4H)-one (224a) was obtained as yellow platelets, (62%), m.p. 175° (from ethanol), ν_{\max} . 1780, 1720 and 1670 (CO) cm⁻¹.

Found: C, 65.5%; H, 4.9%; N, 7.8%.

C₂₀H₁₈N₂O₅ requires: C, 65.6%; H, 4.9%; N, 7.7%.

2.14. Reaction of 2-Cyano-4-hydroxyquinoxalin-3(4H)-one 1-N-Oxide (193a) with Acetic Anhydride.

(a) Mild treatment as above afforded 4-acetoxy-2-cyanoquin-
oxalin-3(4H)-one 1-N-oxide (193b) as yellow needles, (75%),

m.p. 186° (from ethanol), ν_{\max} . 1800 and 1680 cm^{-1} .

Found: C, 54.0%; H, 3.3%; N, 17.5%.

$C_{11}H_7N_3O_4$ requires: C, 53.9%; H, 2.9%; N, 17.1%.

(b) Prolonged treatment, as above, produced darkening but also afforded the acetoxy-compound (193b) (64%).

2.15. Reaction of 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-Oxide (202a) with Benzoyl Chloride.

4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) (0.25 g) was dissolved in 10% aqueous sodium hydroxide (4.0 ml) and shaken with benzoyl chloride (0.4 ml), added in three portions. The reaction mixture was shaken for 10 min to destroy excess benzoyl chloride, then filtered and the product was washed well with water affording 4-benzoyloxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (205) as small, cream needles, (91%), m.p. 205° (from ethanol), ν_{\max} . 1770 and $1670\text{ (CO)}\text{ cm}^{-1}$, τ (CF_3CO_2H) 1.3-2.5 (14H, m, Ar-H).

Found: C, 70.7%; H, 4.6%; N, 8.4%.

$C_{21}H_{14}N_2O_4$ requires: C, 70.4%; H, 3.9%; N, 7.8%.

2.16. Reaction of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (216) and (220b) with Acetic Anhydride.

The 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216) or (220b) (0.5 g) was heated under reflux with acetic anhydride (2.5 ml) for 4.5h. The reaction mixture was evaporated under reduced pressure and the residue was triturated with ether giving a solid which was combined with material obtained by evaporating the mother-liquors and

treatment with water. Crystallisation gave the product (226), ν_{max} . 1765-1745 and 1670-1645 (CO) cm^{-1} , or (224b), ^1H n.m.r. spectra, Table 5.

(i) 6-Acetoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (226a), (78%), had m.p. 126° (lit.,¹⁴⁷ 134°).

(ii) 6-Acetoxy-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (226b) was obtained as a pale orange solid, (90%), m.p. 173° (from ethanol-water).

Found: C, 70.2%; H, 5.1%; N, 8.8%.

$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ requires: C, 70.1%; H, 5.2%; N, 9.1%.

(iii) 6-Acetoxy-7-methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (226c) was obtained as tan plates, (73%), m.p. 188° (from acetic acid-water).

Found: C, 66.2%; H, 5.0%; N, 8.5%.

$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_4$ requires: C, 66.7%; H, 5.0%; N, 8.6%.

(iv) 6-Acetoxy-7-bromo-4-methyl-2-phenylquinoxalin-3(4H)-one (226d) was obtained as yellow, hexagonal plates, (56%), m.p. 167° (from ethanol).

Found: C, 54.7%; H, 3.5%; N, 7.7%.

$\text{C}_{17}\text{H}_{13}\text{BrN}_2\text{O}_3$ requires: C, 54.7%; H, 3.5%; N, 7.5%.

(v) 6-Acetoxy-7-chloro-4-methyl-2-phenylquinoxalin-3(4H)-one (226e) was obtained as a tan solid, (78%), m.p. 171° (from ethanol).

Found: C, 62.7%; H, 4.1%; N, 8.0%.

$\text{C}_{17}\text{H}_{13}\text{ClN}_2\text{O}_3$ requires: C, 62.1%; H, 4.0%; N, 8.5%.

(vi) 6-Acetoxy-4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one (226f) was obtained as yellow needles, (58%), m.p. 194° (from acetic acid-water).

Found: C, 60.7%; H, 3.7%; N, 12.5%.

$C_{17}H_{13}N_3O_5$ requires: C, 60.2%; H, 3.9%; N, 12.4%.

(vii) 6-Acetoxyethyl-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (224b) was obtained as a yellow solid, (80%), m.p. 114° (from ethanol-water), ν_{\max} . 1725 and 1645 (CO) cm^{-1} .

Found: C, 70.6%; H, 5.4%; N, 8.3%.

$C_{19}H_{18}N_2O_3$ requires: C, 70.8%; H, 5.6%; N, 8.7%.

2.17. Reaction of the 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides (220a) and (215f) with Acetic Anhydride.

(a) 6,7-Dimethyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (220a) (0.5 g) was heated under reflux in acetic anhydride (5.0 ml) for 4.5h. The reaction mixture was cooled, triturated with ether and the white solid collected (0.33 g), ν_{\max} . 1760 and 1710 (CO) cm^{-1} . This product was shown to be a mixture by its ^1H n.m.r. spectrum, τ (CDCl_3) 2.00-2.78 (4H, m, Ar-H), 7.29 (6H, s, 2- CH_3) and 7.73 (6H, s, 2- CH_3).

(b) 7-Nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) (0.5 g) was heated under reflux in acetic anhydride (2.5 ml) for 4.5h. The reaction mixture was evaporated and the residue triturated with ether to afford 1,3-diacetyl-5-nitro-benzimidazol-2-one (237b) as pale yellow needles, (quantitative), m.p. 231° (from acetic acid-water), ν_{\max} . 1780 and 1730 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.50-1.67 (2H, m, Ar-H), 2.48 (1H, d, J 9.0 Hz, H-7) and 7.06 (6H, s, 2- CH_3).

Found: C, 50.8%; H, 3.5%; N, 16.8%.

C₁₁H₉N₃O₅ requires: C, 50.2%; H, 3.5%; N, 16.0%.

2.18. Reaction of 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (202) and (210a) with Acetyl Chloride.

The 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202) or (210a) (0.2 g) was heated under reflux with acetyl chloride (2.5 ml) and acetic acid (1.5 ml) for 7h. The resulting solution was evaporated under reduced pressure, and the residue was triturated with ether to afford the product (242a) or (243), ν_{\max} . 1795-1785 (N-OAc) and 1690-1665 (CO) cm^{-1} , ^1H n.m.r. spectra, Table 6.

(i) 4-Acetoxy-6-chloro-2-phenylquinoxalin-3(4H)-one (242a) was obtained as white needles, (90%), m.p. 176° (from ethanol)

Found: C, 61.8%; H, 3.5%; N, 8.7%.

C₁₆H₁₁ClN₂O₃ requires: C, 61.1%; H, 3.5%; N, 8.9%.

Hydrogenation of the compound (242a) afforded 6-chloro-2-phenylquinoxalin-3(4H)-one (204e) identical (mixed m.p. and i.r. spectrum) with a sample obtained by sodium dithionite reduction of 6-chloro-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202e) (see before).

(ii) 4-Acetoxy-8-chloro-6-methyl-2-phenylquinoxalin-3(4H)-one (243a) was obtained as tan needles, (75%), m.p. 167° (from ethanol).

Found: C, 62.4%; H, 4.0%; N, 8.7%.

C₁₇H₁₃ClN₂O₃ requires: C, 62.1%; H, 4.0%; N, 8.5%.

(iii) 4-Acetoxy-8-chloro-6-methoxy-2-phenylquinoxalin-3(4H)-one (243b) was obtained as a tan solid, (58%), m.p. 172° (from

acetic acid-water).

Found: C, 59.0%; H, 3.8%; N, 8.2%.

$C_{17}H_{13}ClN_2O_4$ requires: C, 59.2%; H, 3.8%; N, 8.1%.

(iv) 4-Acetoxy-6-bromo-8-chloro-2-phenylquinoxalin-3(4H)-one (243c) was obtained as cream needles, in quantitative yield, m.p. 198° (from ethanol).

Found: C, 48.8%; H, 2.4%; N, 6.0%.

$C_{16}H_{10}BrClN_2O_3$ requires: C, 48.8%; H, 2.5%; N, 7.1%.

(v) 4-Acetoxy-6,8-dichloro-2-phenylquinoxalin-3(4H)-one (243d) was obtained as cream needles, (60%), m.p. 195° (from ethanol-acetic acid).

Found: C, 55.0%; H, 2.9%; N, 8.5%.

$C_{16}H_{10}Cl_2N_2O_3$ requires: C, 55.0%; H, 2.8%; N, 8.0%.

(vi) Reaction of 6,7-dimethyl-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (210a) afforded a dichloro-derivative as pale yellow needles, (84%), m.p. 260° (from ethanol-acetic acid), ν_{\max} . 1650 (CO) cm^{-1} .

Found: C, 59.9%; H, 3.7%; M^+ , 322, 318.

$C_{16}H_{12}Cl_2N_2O$ requires: C, 60.2%; H, 3.8%; M , 322, 318.

2.19. Reaction of 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides (215) and (220a) with Acetyl Chloride.

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215) or (220a) (0.2 g) was heated under reflux with acetyl chloride (2.5 ml) and acetic acid (1.5 ml) for 7h. The reaction mixture was cooled and any insoluble solid was filtered off and combined with material obtained by evaporating the mother-liquors under

reduced pressure and treatment with a little ether, to give the product (204e), (238), (240a) or (241a), ν_{\max} . 1670-1645 (CO) cm^{-1} , ^1H n.m.r. spectra, Table 5.

(i) 6-Chloro-2-phenylquinoxalin-3(4H)-one (204e), (86%), had m.p. 264° (lit.,¹³⁸ 275°).

(ii) 6-Chloro-7-methyl-2-phenylquinoxalin-3(4H)-one (238b) was obtained as pale yellow plates, in quantitative yield, m.p. 270° (from acetic acid).

Found: C, 66.5%; H, 4.1%; N, 10.3%.

$\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$ requires: C, 66.6%; H, 4.1%; N, 10.4%.

(iii) 6-Chloro-7-methoxy-2-phenylquinoxalin-3(4H)-one (238c), (75%), had m.p. 226° (lit.,¹³⁸ 260°).

(iv) 7-Bromo-6-chloro-2-phenylquinoxalin-3(4H)-one (238d) was obtained as yellow plates, (69%), m.p. 300° (from acetic acid-dimethylformamide).

Found: C, 50.1%; H, 2.4%; N, 8.3%.

$\text{C}_{14}\text{H}_8\text{BrClN}_2\text{O}$ requires: C, 50.1%; H, 2.4%; N, 8.3%.

(v) 6,7-Dichloro-2-phenylquinoxalin-3(4H)-one (238e), (93%), had m.p. 294° (lit.,¹³⁸ 305°).

(vi) Reaction of 7-nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (215f) afforded a mixture, (94%), of 6-chloro-7-nitro-2-phenylquinoxalin-3(4H)-one (238f), (37.5%), and 8-chloro-7-nitro-2-phenylquinoxalin-3(4H)-one (241a), (56.5%), as buff plates, m.p. $285\text{--}295^\circ$ (from glacial acetic acid).

Found: C, 55.6%; H, 2.6%; N, 14.2%.

$\text{C}_{14}\text{H}_8\text{ClN}_3\text{O}_3$ requires: C, 55.1%; H, 2.7%; N, 13.9%.

(vii) 8-Chloro-6,7-dimethyl-2-phenylquinoxalin-3(4H)-one (240a) was obtained as pale yellow needles, (91%), m.p. 274° (from acetic acid-dimethylformamide).

Found: C, 66.8%; H, 4.5%; N, 9.8%.

C₁₆H₁₃ClN₂O requires: C, 67.5%; H, 4.6%; N, 9.8%.

2.20. Reaction of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (216) and (220b) with Acetyl Chloride.

The 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216) or (220b) was reacted with acetyl chloride as above, to give the product (239), (240b) or (241b), ν_{\max} . 1670-1640 (CO) cm⁻¹, ¹H n.m.r. spectra, Table 5.

(i) 6-Chloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239a), (93°), had m.p. 125° (lit.,¹³⁸ 123°).

(ii) 6-Chloro-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (239b) was obtained as pale yellow needles, in quantitative yield, m.p. 162° (from ethanol-acetic acid).

Found: C, 67.4%; H, 4.5%; N, 9.5%.

C₁₆H₁₃ClN₂O requires: C, 67.5%; H, 4.6%; N, 9.8%.

(iii) 6-Chloro-7-methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (239c) was obtained as yellow needles, (70%), m.p. 176° (from ethanol-acetic acid).

Found: C, 64.0%; H, 4.4%; N, 8.9%.

C₁₆H₁₃ClN₂O₂ requires: C, 63.9%; H, 4.3%; N, 9.3%.

(iv) 7-Bromo-6-chloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239d) was obtained as pale yellow needles, (60%), m.p. 174° (from ethanol-acetic acid).

Found: C, 52.0%; H, 2.9%; N, 7.6%.

C₁₅H₁₀BrClN₂O requires: C, 51.5%; H, 2.9%; N, 8.0%.

(v) 6,7-Dichloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239e) was obtained as pale yellow needles, (94%), m.p. 171° (from ethanol-acetic acid).

Found: C, 58.7%; H, 3.6%; N, 9.6%.

C₁₅H₁₀Cl₂N₂O requires: C, 59.0%; H, 3.3%; N, 9.2%.

(vi) Reaction of 4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216f) afforded a mixture, (90%), of 6-chloro-4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one (239f), (54%), and 8-chloro-4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one (241b), (36%), as pale yellow prisms, m.p. 183-190° (from ethanol-acetic acid), T.L.C. over silica in benzene-ether showed two spots, but column chromatography over deactivated alumina and elution with toluene, failed to achieve a separation of the mixture (72% recovery).

Found: C, 57.4%; H, 3.2%; N, 12.9%.

C₁₅H₁₀ClN₃O₃ requires: C, 57.1%; H, 3.2%; N, 13.3%.

(vii) 8-Chloro-2-phenyl-4,6,7-trimethylquinoxalin-3(4H)-one (240b) was obtained as pale yellow needles, in quantitative yield, m.p. 157° (from acetic acid-water).

Found: C, 68.3%; H, 5.0%; N, 8.8%.

C₁₇H₁₅ClN₂O requires: C, 68.3%; H, 5.0%; N, 9.4%.

2.21. Methylation of the 2-Phenylquinoxalin-3(4H)-ones (238), (240a) and (241a).

The 2-phenylquinoxalin-3(4H)-one (238), (240a) or (241a),

(0.15 g), obtained in 2.19. was heated under reflux in anhydrous acetone (15.0 ml) with anhydrous potassium carbonate (0.55 g). Dimethyl sulphate (0.3 ml) was added dropwise and heating was continued for 4h. The reaction mixture was evaporated under reduced pressure, and the residue was treated with water giving an oil, which on chilling and rubbing yielded a yellow solid, identical (mixed m.p. and i.r. spectra) with the methylated product (239), (240b) or (241b) previously obtained.

(i) 6-Chloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239a), (97%), had m.p. 125° (lit.,¹³⁸ 123°).

(ii) 6-Chloro-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (239b), (82%), had m.p. 154° .

(iii) 6-Chloro-7-methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (239c), was obtained in quantitative yield, m.p. 160° .

(iv) 7-Bromo-6-chloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239d), (96%), had m.p. 173° .

(v) 6,7-Dichloro-4-methyl-2-phenylquinoxalin-3(4H)-one (239e), (67%), had m.p. 160° .

(vi) Methylation of the mixture obtained in 2.19 (vi) afforded a mixture, (57%), of 6-chloro-4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one (239f), (23%), and 8-chloro-4-methyl-7-nitro-2-phenylquinoxalin-3(4H)-one (241b), (34%).

(vii) 8-Chloro-2-phenyl-4,6,7-trimethylquinoxalin-3(4H)-one (240b), (91%), had m.p. 152° .

2.22. Attempted Reaction of 2-Cyano-4-methylquinoxalin-3(4H)-one 1-N-Oxide (193d) with Acetyl Chloride.

2-Cyano-4-methylquinoxalin-3(4H)-one 1-N-oxide (193d),¹⁴⁸ heated under reflux with acetyl chloride, as above, was recovered unchanged (85%).

2.23. Reaction of 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides (215a), (216a) and (220b) with Acetyl Bromide.

The 2-phenylquinoxalin-3(4H)-one 1-N-oxide (215a), (216a) or (220b) (0.2 g) was heated under reflux with acetyl bromide (2.5 ml) and glacial acetic acid (1.5 ml) for 7h. The reaction mixture was cooled, evaporated under reduced pressure and the residual yellow solid was washed out with a little ether and crystallised to afford the product.

(a) With fresh acetyl bromide the product was the corresponding deoxygenated 2-phenylquinoxalin-3(4H)-one (204a) or (218a).

(b) With old (red) acetyl bromide the product was the hydrobromide of the corresponding deoxygenated 2-phenylquinoxalin-3(4H)-one (204a), (218a) or (211b). The hydrobromides were converted by treatment with aqueous sodium bicarbonate or by crystallisation from ethanol-water into the compounds (204a), (218a) and (211b).

The old acetyl bromide contained no free bromine as demonstrated by its failure to react with phenol to afford 2,4,6-tribromophenol.

(i) 2-Phenylquinoxalin-3(4H)-one (204a), [(a) 96%; (b) 85%], was identical (m.p., mixed m.p., and i.r. spectrum) with an authentic sample.¹⁴⁹

(ii) 4-Methyl-2-phenylquinoxalin-3(4H)-one (218a), [(a) 80%; (b) quantitative yield], was identical (m.p. mixed m.p., and i.r. spectrum) with an authentic sample.¹⁴⁹

Heating under reflux with fresh acetyl bromide for 17h resulted in a quantitative yield of the compound (218a).

(iii) 2-Phenyl-4,6,7-trimethylquinoxalin-3(4H)-one (211b) was obtained from old acetyl bromide, in quantitative yield, identical (m.p., mixed m.p. and i.r. spectrum) with a sample prepared as described in 2.12.

2.24. Reaction of 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-Oxides (202) with Acetyl Bromide.

The 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202), was reacted with acetyl bromide, as above. The products were obtained as hydrobromides, except in (ii) (see below) and were converted into the free 4-hydroxy-2-phenylquinoxalin-3(4H)-ones (245) by crystallisation from ethanol-water or by treatment with aqueous sodium bicarbonate, ¹H n.m.r. spectra, Table 6.

(i) 4-Hydroxy-2-phenylquinoxalin-3(4H)-one (245a) was obtained as cream needles, (53%), m.p. 206° (from ethanol-water), ν_{\max} . 1670 (CO) cm^{-1} .

Found: C, 70.2%; H, 4.3%; N, 11.9%.

C₁₄H₁₀N₂O₂ requires: C, 70.6%; H, 4.2%; N, 11.7%.

(ii) 4-Acetoxy-6-bromo-2-phenylquinoxalin-3(4H)-one (242b) was obtained as pale yellow needles, (82%), m.p. 161° (from ethanol), ν_{\max} . 1795 and 1680 (CO) cm^{-1} .

Found: C, 54.1%; H, 3.1%; N, 8.1%; M^+ , 360, 358.

$C_{16}H_{11}BrN_2O_3$ requires: C, 53.5%; H, 3.1%; N, 7.8%; M, 360, 358.

(iii) 6-Chloro-4-hydroxy-2-phenylquinoxalin-3(4H)-one (245b)

was obtained as cream needles, in quantitative yield, m.p. 183° (from ethanol-water), ν_{\max} . 1660 (CO) cm^{-1} .

Found: C, 60.6%; H, 3.2%; N, 10.3%.

$C_{14}H_9ClN_2O_2$ requires: C, 61.6%; H, 3.3%; N, 10.3%.

Mild acetylation of this product afforded 4-acetoxy-6-chloro-2-phenylquinoxalin-3(4H)-one (242a), (70%), identical (m.p., mixed m.p., i.r. spectrum and n.m.r. spectrum) with a sample prepared by the reaction of 4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202a) with acetyl chloride (see before).

2.25. Hydrogenolyses of the N-Acetoxyquinoxalin-3(4H)-ones (221a), (203a), (242a), (224a) and (193b).

The N-acetoxyquinoxalin-3(4H)-ones, above, were hydrogenated in ethanol over 10% palladium-charcoal. The reaction mixtures were filtered and the filtrates were evaporated to give the corresponding quinoxalin-3(4H)-ones which were purified by crystallisation.

(i) 6-Acetoxy-2-phenylquinoxalin-3(4H)-one (221b) was obtained by hydrogenation of compound (221a), as cream hexagonal plates, (77%), m.p. 234° (from ethanol), ν_{\max} . 3300 (NH), 1750 and 1655 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.72-2.32 (6H, m, Ar-H), 2.34 (1H, d, J 2.0 Hz, H-5), 2.49 (1H, dd, J_o 9.0 Hz, J_m 2.0 Hz, H-7), and 7.48 (3H, s, OAc).

(ii) 2-Phenylquinoxalin-3(4H)-one (204a) was obtained by

hydrogenation of 4-acetoxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (203a), (71%), m.p. 250°, identical (mixed m.p. and i.r. spectrum) with an authentic sample.¹⁴⁹

(iii) 6-Chloro-2-phenylquinoxalin-3(4H)-one (204e) was obtained by hydrogenation of 4-acetoxy-6-chloro-2-phenylquinoxalin-3(4H)-one (242a), (62%), identical (mixed m.p. and i.r. spectrum) with a sample obtained by sodium dithionite reduction of 6-chloro-4-hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-oxide (202e).

(iv) 6-Acetoxymethyl-7-methyl-2-phenylquinoxalin-3(4H)-one (224c) was obtained by hydrogenation of 4-acetoxy-6-acetoxy-methyl-7-methyl-2-phenylquinoxalin-3(4H)-one (224a), as cream needles, (72%), m.p. 230° (from ethanol), ν_{\max} . 1735 and 1660 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.70-1.82 (2H, m, Ar-H), 1.97 (1H, s, H-8), 2.08-2.35 (4H, m, Ar-H), 4.52 (2H, s, CH_2), 7.41 (3H, s, CH_3), and 7.66 (3H, s, CH_3).

Found: C, 70.5%; H, 5.3%; N, 9.2%.

$\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$ requires: C, 70.1%; H, 5.2%; N, 9.1%.

(v) Quinoxalin-3(4H)-one (194) was obtained by hydrogenation of 4-acetoxy-2-cyanoquinoxalin-3(4H)-one 1-N-oxide (193b), (85%), and was identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample.¹⁴⁸

2.26. Hydrolysis of 6-Acetoxy-2-phenylquinoxalin-3(4H)-ones (221a) (226a-c) and (224b)

The 6-acetoxy-2-phenylquinoxalin-3(4H)-one (221a), (226a-c) or (224b) (0.5 g) was heated with 10% aqueous sodium hydroxide (20.0 ml) on a boiling water bath for 2h. The reaction mixture was cooled and acidified with 25% (v/v) aqueous

hydrochloric acid. The precipitated 6-hydroxy-2-phenylquinoxalin-3(4H)-one (246a), (227) or (228) was filtered off and washed with cold water.

(i) 6-Hydroxy-2-phenylquinoxalin-3(4H)-one (246a) was obtained by hydrolysis of compound (221a), as buff needles in quantitative yield, m.p. 286° (decomp.) (from ethanol-water), ν_{\max} . 3250 (OH), 1640 (CO) and 1620 cm^{-1} .

Found: C, 70.6%; H, 4.2%; N, 11.4%.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$ requires: C, 70.6%; H, 4.2%; N, 11.8%.

(ii) 6-Hydroxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227a) was obtained by hydrolysis of compound (226a), (97%), m.p. $305-310^{\circ}$ (lit., $^{147} 300^{\circ}$), ν_{\max} . 3250 (OH), 1640 (CO) and 1620 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.88-2.40 (6H, m, Ar-H), 2.66 (1H, dd, J_{O} 8.5 Hz, J_{m} 2.25 Hz, H-7), 2.68 (1H, d, J 2.25 Hz, H-5), and 5.98 (3H, s, CH_3).

(iii) 4,7-Dimethyl-6-hydroxy-2-phenylquinoxalin-3(4H)-one (227b) was obtained by hydrolysis of compound (226b), as pale yellow needles, in quantitative yield, m.p. 274° (from glacial acetic acid), ν_{\max} . 3200 (OH) and 1620 cm^{-1} (CO), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.95-2.40 (6H, m, Ar-H), 2.69 (1H, s, H-5), 5.97 (3H, s, N- CH_3), and 7.42 (3H, s, C- CH_3).

Found: C, 72.5%; H, 5.3%; N, 10.1%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

(iv) 6-Hydroxy-7-methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227c) was obtained by hydrolysis of compound (226c) as a yellow solid in quantitative yield, m.p. 216° (from acetic acid-water), ν_{\max} . 3300-3200 br (OH), and 1620 cm^{-1} (CO),

τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.94-2.36 (5H, m, Ar-H), 2.40 (1H, s, H-8), 2.59 (1H, s, H-5), 5.88 (3H, s, CH_3), and 5.92 (3H, s, CH_3).

Found: C, 68.5%; H, 5.0%; N, 9.4%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

(v) 4,7-Dimethyl-6-hydroxymethyl-2-phenylquinoxalin-3(4H)-one (228) was obtained, without acidification by hydrolysis of 6-acetoxymethyl-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (224b), as yellow plates, (97%), m.p. 133° (from ethanol-water), ν_{max} . 3400-3300 br (OH) and 1620 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.85-1.95 (3H, m, Ar-H), 2.02 (1H, s, H-5 or H-8), 2.10-2.38 (3H, m, Ar-H), 4.82 (2H, s, CH_2), 5.89 (3H, s, N- CH_3), and 7.48 (3H, s, C- CH_3).

Found: C, 71.0%; H, 5.4%; N, 10.0%.

$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$ requires: C, 72.8%; H, 5.8%; N, 10.0%.

2.27. Methylation of 2-Phenylquinoxalin-3(4H)-ones (204c-d) and (224c) and 6-Hydroxy-2-phenylquinoxalin-3(4H)-ones (246a) and (227).

The 2-phenylquinoxalin-3(4H)-ones (204c-d) and (224c) and the 6-hydroxy-2-phenylquinoxalin-3(4H)-ones (246a) and (227) were methylated by heating with dimethyl sulphate (0.3 ml per replaceable hydrogen) as in 2.21 above, to afford the corresponding methylated compounds (246b), (247), (248) and (224b).

(i) 6-Methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (246b).

(a) Methylation of 6-hydroxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227a) afforded compound (246b), (91%), m.p. 96° (lit., ¹⁴⁷ 96°), ν_{max} . 1650 (CO) and 1610 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.83-2.40 (6H, m, Ar-H), 2.61 (1H, dd, J_o 9.0 Hz, J_m 2.0 Hz, H-7), 2.75 (1H, d, J 2.0 Hz, H-5), 5.89 (3H, s, CH_3), and

5.93 (3H, s, CH₃).

(b) Methylation of 6-hydroxy-2-phenylquinoxalin-3(4H)-one (246a) afforded compound (246b), (71%), m.p. 83-90°, identical (mixed m.p. and i.r. spectrum) with a sample obtained as above.

(c) Methylation of 6-methoxy-2-phenylquinoxalin-3(4H)-one (204c) afforded compound (246b), (77%), m.p. 95°, identical (mixed m.p. and i.r. spectrum) with a sample obtained as above.

(ii) 6-Bromo-4-methyl-2-phenylquinoxalin-3(4H)-one (247) was obtained by methylation of 6-bromo-2-phenylquinoxalin-3(4H)-one (204d) as pale yellow needles, (70%), m.p. 139° (from ethanol), ν_{\max} . 1640 (CO) cm⁻¹, τ (CF₃CO₂H) 1.85-2.40 (8H, m, Ar-H), 5.96 (3H, s, CH₃).

Found: C, 57.3%; H, 3.6%; N, 8.5%.

C₁₅H₁₁BrN₂O requires: C, 57.2%; H, 3.5%; N, 8.9%.

(iii) 6,7-Dimethoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (248) was obtained by methylation of 6-hydroxy-7-methoxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227c) as yellow plates, (51%), m.p. 146° (from ethanol), ν_{\max} . 1650 (CO) and 1620 cm⁻¹, τ (CF₃CO₂H) 1.92-2.36 (6H, m, Ar-H), 2.70 (1H, s, H-5), 5.77 (3H, s, N-CH₃), 5.85 (3H, s, OCH₃), and 5.88 (3H, s, OCH₃).

Found: C, 69.0%; H, 5.3%; N, 9.2%.

C₁₇H₁₆N₂O₃ requires: C, 68.9%; H, 5.4%; N, 9.5%.

(iv) 6-Acetoxymethyl-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (224b) was obtained by methylation of 6-acetoxymethyl-7-methyl-2-phenylquinoxalin-3(4H)-one (224c), (64%), m.p. 112°,

identical (mixed m.p. and i.r. spectrum) with a sample obtained by the reaction of 2-phenyl-4,6,7-trimethylquinoxalin-3(4H)-one 1-N-oxide (220b) with acetic anhydride (see above).

2.28. Attempted Oxidation of 4,7-Dimethyl-6-hydroxymethyl-2-phenylquinoxalin-3(4H)-one (228).

(a) Hydrogen Peroxide -10% Aqueous Sodium Hydroxide.

The hydroxymethyl compound (228) was suspended in 10% aqueous sodium hydroxide (10.0 ml) and 30% (v/v) aqueous hydrogen peroxide (10.0 ml) was added in one portion.

(i) The reaction mixture was stirred at room temperature for 22h. Filtration afforded unchanged starting material (75%).

(ii) The reaction mixture was heated under reflux for 2.5h. Filtration afforded unchanged starting material (64%).

No further material was obtained by acidification of the filtrate from either (i) or (ii).

(b) Manganese Dioxide.

The hydroxymethyl compound (228) (0.2 g) was heated under reflux in acetone (20.0 ml) with activated manganese dioxide (0.6 g) for 3.5h or for 24h. Hot filtration of the reaction mixture and evaporation of the filtrate afforded unchanged starting material (67%).

2.29. Attempted Synthesis of 6-Acetoxymethyl-4,7-dimethyl-2-phenylquinoxalin-3(4H)-one (224b).

(a)(i) Nitration¹⁶¹ of *o*-Toluic Acid.

o-Toluic acid (50.0 g) was added slowly (1.5h) with stirring to fuming nitric acid (150 ml) cooled in an ice-bath.

Stirring was continued for a further 1.5h, the yellow solution was poured onto ice and the white precipitate collected and dried. The product, (91%) had m.p. $145-6^{\circ}$ (lit.,¹⁶¹ $145-6^{\circ}$) and was shown by its ^1H n.m.r. spectrum, τ ($\text{CF}_3\text{CO}_2\text{H}$) [compound (231a)] 1.01 (1H, d, J 2.5 Hz, H-3), 1.61 (1H, dd, J_{O} 8.5 Hz, J_{m} 2.5 Hz, H-5), 2.41 (1H, d, J 8.0 Hz, H-6), and 7.17 (3H, s, CH_3); [compound (232a)] 1.73 (1H, dd, J_{O} 8.5 Hz, J_{m} 1.5 Hz, H-5), 1.98 (1H, dd, J_{O} 8.0 Hz, J_{m} 1.5 Hz, H-3), 2.49 (1H, t, J 8.0 Hz, H-4), and 7.28 (3H, s, CH_3) to be a mixture of the isomers 4-nitro-o-toluic acid (231a) (52%), and 6-nitro-o-toluic acid (232a) (39%). Attempted separation of the mixture by fractional crystallisation from ethanol-water or from water alone was unsuccessful.

(ii) Esterification of the Mixture of Acids (231a) and (232a).

The mixture of nitro-o-toluic acids (231a) and (232a) (27.0 g) was heated under reflux with ethanol (170 ml) and concentrated sulphuric acid (17.0 ml) for 6h. The reaction mixture was concentrated to ca. one-third volume and was poured onto ice. The oil which separated was extracted into ether, and the extract was washed with saturated aqueous sodium bicarbonate and water. The sodium bicarbonate washings were acidified giving a white precipitate (1.25 g, 4.5%), identical (^1H n.m.r. spectrum) with the starting acid mixture.

Evaporation of the dried (MgSO_4) ether extract gave a yellow oil, (26.85 g, 85%), ν_{max} . 1720 (CO), and 1540 and 1360 (NO_2) cm^{-1} . This was a mixture (as shown by the ^1H n.m.r. spectrum) of the isomeric esters (231b) and (232b) in the ratio 4:3.

The G.L.C. trace obtained from a Pye 104 flame-ionisation

instrument, on a 2.5% silicone elastomer column, at 150°, with hydrogen at 17 p.s.i. indicated that the retention times were too close to achieve separation on a preparative scale. Separation was achieved by distillation using the spinning-band technique to give almost pure ethyl 6-nitro-o-toluate (232b) (9.15 g), b.p. 172°/18 mm, τ (CF₃CO₂H) 1.99 (1H, dd, J_o 8.0 Hz, J_m 1.5 Hz, H-5), 2.11 (1H, dd, J_o 8.0 Hz, J_m 1.5 Hz, H-3), 2.56 (1H, t, J 8.0 Hz, H-4), 5.43 (2H, q, J 7.0 Hz, CH₂), 7.42 (3H, s, CH₃), and 8.49 (3H, t, J 7.0 Hz, CH₂CH₃); a mixture (1:1) of isomers (232b) and (231b) (4.82 g); almost pure (impurity \leq 10%) ethyl 4-nitro-o-toluate (231b) (5.83 g); and pure ethyl-4-nitro-o-toluate (231b) (4.23 g), b.p. 185°/20 mm, m.p. 31°, ν_{\max} . 1720 (CO) and, 1540 and 1360 (NO₂) cm⁻¹, τ (CF₃CO₂H) 1.28 (1H, d, J 2.5 Hz, H-3), 1.77 (1H, dd, J_o 8.5 Hz, J_m 2.5 Hz, H-5), 2.51 (1H, d, J 8.5 Hz, H-6), 5.43 (2H, q, J 7.0 Hz, CH₂), 7.28 (3H, s, CH₃), and 8.48 (3H, t, J 7.0 Hz, CH₂CH₃).

Found: C, 57.5%; H, 5.1%; N, 6.6%.

C₁₀H₁₁NO₄ requires: C, 57.4%; H, 5.3%; N, 6.7%.

(iii) Reduction of Ethyl 4-Nitro-o-toluate (231b).

Ethyl-4-nitro-o-toluate (231b) (4.0 g) was heated under reflux in glacial acetic acid (200 ml) with iron filings (20.0 g) for 1h. The reaction mixture was filtered hot, the filtrate was evaporated under reduced pressure and the residue was washed with water. The crude solid (3.7 g) obtained was stirred in dilute sulphuric acid (10.0 ml) for 10 min. Filtration afforded ethyl-4-acetylamino-o-toluate (233b) (2.14 g, 51%), as white platelets, m.p. 121° (from

ethanol-water), ν_{\max} . 3300 (NH), 1720 and 1660 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.70 (1H, s, NH), 1.11 (1H, d, J 2.25 Hz, H-3), 1.39 (1H, dd, J_o 8.0 Hz, J_m 2.25 Hz, H-5), 1.61 (1H, d, J 8.0 Hz, H-6), 5.46 (2H, q, J 7.0 Hz, CH_2), 7.38 (3H, s, CH_3), and 8.51 (3H, t, J 7.0 Hz, CH_2CH_3).

Found: C, 64.9%; H, 6.6%; N, 6.9%; M^+ , 221.

$\text{C}_{12}\text{H}_{15}\text{NO}_3$ requires: C, 65.1%; H, 6.8%; N, 6.3%; M, 221.

Neutralisation of the acid washings with 10% aqueous sodium hydroxide afforded ethyl 4-amino-o-toluate (233a) (1.2 g, 24%) as a cream solid, ν_{\max} . 3450 and 3400 (NH) and 1715 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.15 (2H, br s, NH_2), 1.84 (1H, br s, H-3), 2.44 (2H, m, H-5 and H-6), 5.45 (2H, q, J 7.0 Hz, CH_2), 7.31 (3H, s, CH_3), and 8.49 (3H, t, J 7.0 Hz, CH_2CH_3). On warming with acetic anhydride the amine (233a) afforded the acetylamino compound (233b).

(iv) Nitration of Ethyl 4-Acetylamino-o-toluate (233b).

Ethyl 4-acetylamino-o-toluate (233b) (1.1 g) was dissolved with stirring in concentrated sulphuric acid (9.25 ml) giving a very dark solution which was cooled to -9° . A mixture of concentrated sulphuric acid (1.2 ml) and concentrated nitric acid (0.35 ml) was added dropwise and stirring was continued for 1.5h. The reaction mixture was poured onto ice giving a gummy, yellow precipitate. Chloroform extraction gave a semi-solid which solidified on trituration with ether to afford a yellow solid (0.8 g, 60%), T.L.C. over silica in benzene-ether (2:1) showed three spots. The ^1H n.m.r. spectrum indicated a mixture of the

mono-nitro isomers, ethyl 4-acetylamino-5-nitro-o-toluate (234) (10%), τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.90 (1H, s, H-6), 2.76 (1H, s, H-3), 5.64 (2H, q, J 7.0 Hz, CH_2), 7.45 (3H, s, CH_3), 7.73 (3H, s, COCH_3), and 8.65 (3H, t, J 7.0 Hz, CH_2CH_3); ethyl 4-acetylamino-3-nitro-o-toluate (235) (30%), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.65 (1H, d, J 9.0 Hz, H-6), 2.62 (1H, d, J 9.0 Hz, H-5), 5.64 (2H, q, J 7.0 Hz, CH_2), 7.66 (3H, s, CH_3), 7.79 (3H, s, COCH_3), and 8.65 (3H, t, J 7.0 Hz, CH_2CH_3); and ethyl 4-acetylamino-6-nitro-o-toluate (236) (20%), τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.88 (1H, d, J 2.0 Hz, H-5), 1.98 (1H, d, J 2.0 Hz, H-3), 5.64 (2H, q, J 7.0 Hz, CH_2), 7.50 (3H, s, CH_3), 7.85 (3H, s, COCH_3), and 8.65 (3H, t, J 7.0 Hz, CH_2CH_3). Column chromatography over deactivated alumina, and elution with toluene failed to effect a separation of the isomer mixture.

Nitration of the compound (233b) as above but at room temperature afforded the same isomer mixture (37%).

2.30. Attempted Reaction of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxide (216a) with Potassium Cyanide and Ethyl Cyanoacetate.

(a) Potassium Cyanide.

(i) A solution of potassium cyanide (3.0 g) in water (30.0 ml) was added to a solution of 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) (0.75 g) in chloroform (30.0 ml) and the mixture was cooled to 0° . A solution of benzoyl chloride (0.5 ml) in chloroform (2.0 ml) was added dropwise with stirring. Stirring was continued for 10 min and the chloroform layer was separated, dried (MgSO_4) and evaporated. The gummy residue was triturated with ether yielding unchanged

starting material (41% recovery).

(ii) Potassium cyanide (0.004 mol) and acetic anhydride (0.002 mol) were added to a solution of 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) (0.001 mol) in dimethylsulphoxide (5.0 ml) and the reaction mixture was heated under reflux for 4h. Dilution with water and chloroform extraction afforded an intractable oil.

(b) Ethyl Cyanoacetate.

A solution of 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) (0.001 mol) in chloroform (5.0 ml) was treated with acetic anhydride (0.001 mol) and ethyl cyanoacetate (0.001 mol). The reaction mixture was stirred at room temperature for 2h and heated on a water bath at 100° for 2h. Evaporation afforded unchanged N-oxide (92% recovery).

2.31. Attempted Reaction of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxide-Boron Trifluoride Complex (249) with Ethyl Cyanoacetate.

(a) 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide-boron trifluoride complex (249).

Boron trifluoride etherate (0.5 ml) was added dropwise with stirring at room temperature to a solution of 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) (0.0025 mol) in chloroform (5.0 ml). After 30 min. at room temperature the yellow crystalline precipitate was filtered (0.72 g, 90%), ν_{\max} . 1640 cm^{-1} . The complex was unstable to crystallisation from ethanol, reverting to the N-oxide (216a).

(b) Ethyl cyanoacetate (0.0025 mol) was added to a suspension

of the boron trifluoride complex (249) in chloroform and the mixture was heated at 60-65° on a water bath for 3.5h.

Filtration afforded unchanged boron trifluoride complex (50%). Evaporation of the filtrate gave an oil which yielded the N-oxide (216a) (28%) on trituration with methanol-ether.

2.32. Attempted Reaction of 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-Oxide-Acetoxonium Perchlorate (250) with Lithium Acetate and Lithium Chloride.

(a) 4-Methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide-acetoxonium perchlorate (250).

Acetic anhydride (6.0 ml, large excess) and perchloric acid (0.5 ml) were added to a solution of 4-methyl-2-phenylquinoxalin-3(4H)-one 1-N-oxide (216a) (0.002 mol) in glacial acetic acid (3.0 ml) at 0° and the reaction mixture was stirred for 2h. A yellow solid (0.54 g) slowly separated out and was washed with ether.

Attempted conversion of this yellow solid into the N-oxide (216a) with dilute ammonium hydroxide only yielded 6-hydroxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227a) identical with a sample obtained, as above.

(b) Lithium Acetate.

A solution of the perchlorate (250) (0.35 g) in acetonitrile (10.0 ml) was stirred at room temperature for 18h with lithium acetate (0.3 g, threefold excess). The reaction mixture was filtered to remove inorganic salts and evaporated to afford a dark gum which was extracted into chloroform and washed with 10% aqueous sodium hydroxide.

Acidification of the aqueous phase afforded 6-hydroxy-4-methyl-2-phenylquinoxalin-3(4H)-one (227a) (0.05 g) and evaporation of the dried (MgSO_4) chloroform extract afforded the N-oxide (216a) (0.05 g).

(c) Lithium Chloride.

Attempted reaction with lithium chloride as in (b), but with heating under reflux for 2h, afforded compound (227a) (0.1 g) and the N-oxide (216a) (0.05 g).

Table 3.

Assignments^{a,b} (τ) of ^1H n.m.r. Resonance Signals of 2-Phenylquinoxalin-3(4H)-ones and their 1-N-Oxides.

Compd.	H(5)	H(6)	H(7)	H(8)	C CH ₃	N CH ₃	O CH ₃	Ar-H
(215b)	2.45d	2.24dd	-	1.65s	7.41s	-	-	2.38m
(215c)	← 2.25 - 2.45m ^g →	-	-	1.98s	-	-	5.98s	2.25 - 2.45 m ^g
(215d)	2.49d	2.03dd	-	1.31d	-	-	-	2.39s
(215e)	2.52d	2.17dd	-	1.47d	-	-	-	2.38s
(215f)	2.20d	1.31dd	-	0.53d	-	-	-	2.28 - 2.40 m
(220a)	2.51s	-	-	1.70s	7.46s) 7.48s)	-	-	2.38s
(216b)	2.31d	2.15dd	-	1.59s	7.41s	6.00s	-	2.38s
(216c)	← 2.24 - 2.39m ^g →	-	-	1.92d	-	← 5.98d →	-	2.24 - 2.39m ^g
(216d)	2.37d	1.97dd	-	1.24d	-	6.04s	-	2.42s
(216e)	2.33d	2.12dd	-	1.42d	-	6.07s	-	2.42s
(216f)	2.06d	1.25dd	-	0.63d	-	5.99s	-	2.36s
(220b)	2.39s ^h	-	-	1.65s	7.40s) 7.48s)	6.00s	-	2.39s ^h
(217b)	← 1.73 - 2.40m ^g →	-	-	2.01s	7.39s	-	-	1.73 - 2.40m ^g
(217c)	← 1.72 - 2.40 m ^g →	-	-	2.03s	-	-	6.01s	1.72 - 2.40m ^g
(217d)	2.39d	1.95dd	-	1.65d	-	-	-	1.71 - 2.29m
(217e)	← 1.71 - 2.37m ⁱ →	-	-	1.71 - 2.37 m ⁱ	-	-	-	1.71 - 2.37m ⁱ
(204a)	← 1.70 - 2.25m ^j →	-	-	-	-	-	-	1.70 - 2.25m ^j
(204b)	2.34d	-	1.88 - 2.37m ^c	1.92d	7.33s	-	-	1.88 - 2.37m ^c
(204c)	2.81d	-	2.64dd	1.80 - 2.39m ^k	-	-	5.93s	1.80 - 2.39m ^k
(204d)	1.60 - 2.40m ⁱ	-	← 1.60 - 2.40m ⁱ →	-	-	-	-	1.60 - 2.40m ⁱ
(204e)	1.70 - 2.32m ⁱ	-	← 1.70 - 2.32m ⁱ →	-	-	-	-	1.70 - 2.32m ⁱ
(211a)	2.44s	-	-	2.09s	7.42s) 7.48s)	-	-	1.76 - 2.32m
(218a)	← 1.74 - 2.40m ^j →	-	-	-	-	5.90s	-	1.74 - 2.40m ^j
(218b)	← 1.84 - 2.36m ^g →	-	-	2.02s	7.40s	5.90s	-	1.84 - 2.36m ^g
(218c)	← 1.82 - 2.38m ⁱ →	-	-	1.82 - 2.38m ⁱ	-	5.88s	5.99s	1.82 - 2.38m ⁱ
(218d)	← 1.80 - 2.40m ^g →	-	-	1.65d	-	5.95s	-	1.80 - 2.40m ^g
(218e)	← 1.80 - 2.36m ⁱ →	-	-	1.80 - 2.36m ⁱ	-	5.92s	-	1.80 - 2.36m ⁱ
(211b)	1.88 - 2.32m ^h	-	-	2.08s	7.38s) 7.49s)	5.92s	-	1.88 - 2.32m ^h

a - k See Notes after Table 6, page 203.

Table 4

Assignments^{a,b} (τ) of ^1H n.m.r. Resonance Signals of 3-Cyano-2-phenylquinoxaline 1,4-di-N-oxides, and 4-Hydroxy- and 4-Acetoxy-2-phenylquinoxalin-3(4H)-one 1-N-Oxides.

Cmpd.	H(5)	H(6)	H(7)	H(8)	C CH ₃	O CH ₃	N·OAc	Ar-H
(199a)	1.26td ^f	← 1.78qd →		1.26td ^f	-	-	-	2.26m
(199b)	1.45s	-	1.84dd	1.30d	7.22s	-	-	2.24s
(199c)	1.99d	-	2.12dd	1.32d	-	5.87s	-	2.30s
(199d)	1.12d	-	1.67dd	1.33d	-	-	-	2.30s
(199e)	1.36d	-	1.85dd	1.27d	-	-	-	2.29s
(209a)	1.53s	-	-	1.47s	7.32d	-	-	2.25s
(209b)	1.97s	-	-	1.91s	-	5.74s) 5.77s)	-	2.27s
(202a)	← 1.80 - 2.40m ^e →			1.37d	-	-	-	1.80 - 2.40m ^e
(202b)	1.98s	-	2.24 - 2.40m ^c	1.51d	7.28s	-	-	2.24 - 2.40m ^c
(202c)	2.46d	-	2.63dd	1.52d	-	5.91s	-	2.37s
(202d)	1.67s	-	2.14d	1.54d	-	-	-	2.35s
(202e)	1.90d	-	2.32dd	1.48d	-	-	-	2.36s
(210a)	2.03s	-	-	1.64s	7.33s) 7.45s)	-	-	2.35m
(203a)	← 1.85 - 2.40m ^e →			1.38dd	-	-	7.42s	1.85 - 2.40m ^e
(203b)	2.59s	-	2.25 - 2.45m ^c	1.54d	7.38s	-	7.41s	2.25 - 2.45m ^c
(203c)	2.93d	-	2.66dd	1.44d	-	5.95s	7.40s	2.36s
(203d)	2.24d	-	2.21dd	1.55d	-	-	7.42s	2.35s
(203e)	2.30 - 2.40m ^d	-	2.30 - 2.40m ^d	1.42d	-	-	7.40s	2.30 - 2.40m ^d
(210b)	2.58s	-	-	1.61s	7.45s) 7.48s)	-	7.40s	2.33m

a - f See Notes after Table 6, page 203.

Table 5

Assignment^{a,b} (τ) of ^1H n.m.r. Resonance Signals of the Products obtained by Reaction of the 2-Phenylquinoxalin-3(4H)-one 1-N-Oxides with Acetic Anhydride and Acetyl Chloride.

Compd.	H(5)	H(8)	C-CH ₃	C-OAc	N CH ₃ ^p O CH ₃ ^q	Ar-H, others
(226a)	1.83 - 2.32m ^h	1.74d	-	7.49s	5.98s ^p	1.83 - 3.2m ^h 2.54dd ^s
(226b)	1.88 - 2.30m ^h	1.83s	7.44s	7.55s	5.93s ^p	1.88 - 2.30m ^h
(226c)	← 1.83 - 2.32m ^l →	-	-	7.48s	5.93s ^{p,q} 5.96s)	1.83 - 2.32m ^l
(226d)	2.31s	1.52s	-	7.44s	6.00s ^p	1.83 - 2.24m
(226e)	2.27s	1.64s	-	7.45s	5.98s ^p	1.80 - 2.36m
(226f)	2.38s	1.01s	-	7.48s	6.03s ^p	1.88 - 2.30m
(224b)	2.04s	1.95s	7.39s	7.66s	5.88s ^p	1.80 - 2.36m 4.47s ^r
(238b)	1.71 - 2.34m ^h	1.95s	7.39s	-	-	1.71 - 2.34m ^h
(238c)	1.78 - 2.40m ^h	2.16s	-	-	5.92s ^q	1.78 - 2.40m ^h
(238d)	2.17s	1.57s	-	-	-	1.77 - 2.40m
(238e)	2.13s	1.71s	-	-	-	1.73 - 2.36m
(240a)	2.08s	-	7.33s) 7.42s)	-	-	1.72 - 2.37m
(239a)	← 1.73 - 2.41m ^m →	-	-	-	5.95s ^p	1.73 - 2.41m ^m
(239b)	2.11s	1.94s	7.41s	-	5.97s ^p	1.84 - 2.38m
(239c)	1.86 - 2.40m ^h	2.07s	-	-	5.91s ^{p,q} 6.00s)	1.86 - 2.40m ^h
(239d)	2.06s	1.53s	-	-	5.98s ^p	1.86 - 2.40m
(239e)	2.03s	1.68s	-	-	5.96s ^p	1.82 - 2.37m
(239f)	2.08s	1.20s	-	-	6.00s ^p	1.88 - 2.46m
(241b)	1.72d	-	-	-	6.00s ^p	1.88 - 2.46m ⁿ
(240b)	1.88 - 2.34m ^h	-	7.31s) 7.42s)	-	5.67s ^p	1.88 - 2.34m ^h

a - s See Notes after Table 6, page 203.

Table 6.

Assignments^{a,b} (τ) of ^1H n.m.r. Resonance Signals of the Products Obtained by Reactions of the 4-Hydroxy-2-phenylquinoxalin-3(4H)-one 1-N-Oxides with Acetic Anhydride, Acetyl Chloride and Acetyl Bromide.

Compd.	H(5)	H(7)	H(8)	C-CH ₃	C-OAc	N-OAc	O-CH ₃	Ar - H, Others
(221a) ^t	$\longleftrightarrow 1.60 - 2.92\text{m}^{\text{d}} \longrightarrow$		2.02d	-	7.67s	7.50s	-	1.60 - 2.92m ^d
(223)	$\longleftrightarrow 1.66 - 2.34\text{m}^{\text{m}} \longrightarrow$			-	7.68s	7.34s	-	1.66 - 2.34m ^m 4.52s ^r
(222b)	2.78d	3.02d	-	-	7.42s	7.35s	5.94s	1.96 - 2.39m
(222c)	1.93d	2.00d	-	-	7.43s	7.39s	-	2.35 - 2.48m
(222d)	1.94d	2.00d	-	-	7.41s	7.38s	-	2.40 - 2.58m
(224a)	1.77 - 2.29m ^h	-	1.89s	7.38s	7.69s	7.34s	-	1.77 - 2.29m ^h 4.52s ^r
(242a)	$\longleftrightarrow 1.75 - 2.38\text{m}^{\text{m}} \longrightarrow$			-	-	7.36s	-	1.75 - 2.38m ^m
(243a)	1.88d	1.78 - 2.45m ^c	-	7.36s	-	7.32s	-	1.78 - 2.45m ^c
(243b)	2.57d	2.99d	-	-	-	7.37s	5.94s	1.84 - 2.34m
(243c)	1.85d	2.16d	-	-	-	7.40s	-	1.88 - 2.44m
(243d)	$\left. \begin{array}{l} 2.31\text{d} \\ 1.83\text{d}^{\text{u}} \end{array} \right\}$	$\left. \begin{array}{l} 2.53\text{d} \\ 1.91\text{d}^{\text{u}} \end{array} \right\}$	$\left. \begin{array}{l} - \\ - \end{array} \right\}$	$\left. \begin{array}{l} - \\ - \end{array} \right\}$	$\left. \begin{array}{l} - \\ - \end{array} \right\}$	$\left. \begin{array}{l} 7.36\text{s} \\ 7.10\text{s}^{\text{u}} \end{array} \right\}$	$\left. \begin{array}{l} - \\ - \end{array} \right\}$	$\left. \begin{array}{l} 1.85 - 2.41\text{m} \\ 1.32 - 2.17\text{m}^{\text{u}} \end{array} \right\}$
(245a)	$\longleftrightarrow 1.70 - 2.28\text{m}^{\text{j}} \longrightarrow$			-	-	-	-	1.70 - 2.28m ^j
(245b)	$\longleftrightarrow 1.73 - 2.34\text{m}^{\text{m}} \longrightarrow$			-	-	-	-	1.73 - 2.34m ^m
(242b)	2.13s	1.80 - 2.24m ^c	1.90s	-	-	7.37s	-	1.80 - 2.24m ^c

a - u See Notes after Table 6, page 203.

Notes to Tables 3-6.

- ^a Spectra taken at 100 MHz in trifluoroacetic acid at 28° with tetramethylsilane as internal standard. Chemical shifts are given in p.p.m. downfield from tetramethylsilane to the centre of multiplets and are measured to an accuracy of ± 0.01 p.p.m; s = singlet; d = doublet; dd = double doublet; td = triple doublet; qd = quintuplet of doublets; m = multiplet.
- ^b J_o and J_m were in the ranges 8.5 - 9.5 and 1.5 - 2.5 Hz respectively.
- ^c Ph(H) - H(7); ^d Ph(H) - H(5) - H(7);
- ^e Ph(H) - H(5) - H(6) - H(7); ^f H(5) - H(8);
- ^g Ph(H) - H(5) - H(6); ^h Ph(H) - H(5);
- ⁱ Ph(H) - H(5) - H(6) - H(8);
- ^j Ph(H) - H(5) - H(6) - H(7) - H(8); ^k Ph(H) - H(8);
- ^l Ph(H) - H(5) - H(8); ^m Ph(H) - H(5) - H(7) - H(8);
- ⁿ Ph(H) - H(6); ^p NCH₃; ^q OCH₃;
- ^r CH₂; ^s H(7).
- ^t spectrum taken in CDCl₃
- ^u spectrum taken in DMSO-d₆.

SECTION THREE

3.1. Preparation of Quinoxalin-3(4H)-one 1-N-Oxides (270a-b).

(a) Quinoxalin-3(4H)-one 1-N-oxide (270a).

α -Benzoyl-2-nitroacetanilide was cyclised by the method of Tennant¹³⁴ to give compound (270a), (73%), m.p. 256° (lit.,¹³⁴ 276°).

(b) 4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b).

Methylation of quinoxalin-3(4H)-one 1-N-oxide (270a) by shaking in methanol with methyl iodide and 4% aqueous sodium hydroxide¹³⁴ afforded compound (270b), (81%), m.p. 209° (lit.,¹³⁴ 216°).

3.2. Reaction of the Quinoxalin-3(4H)-one 1-N-Oxides (270a-b) with Aryl Isocyanates.

(a) Quinoxalin-3(4H)-one 1-N-oxide (270a) (0.005 mol) was heated under reflux with (i) phenyl isocyanate, or (ii) *p*-chlorophenyl isocyanate (0.0055 mol) in dimethylformamide (20.0 ml) for 4h. The reaction mixtures were filtered hot to remove trace amounts (< 1%) of insoluble impurities, then cooled and diluted with water to afford -

(i) 2-(N-Phenylamino)quinoxalin-3(4H)-one (271a) as buff needles, (99%), m.p. 252° (from ethanol) (lit.,¹⁷⁰ 248°), ν_{\max} . 3300 (NH) and 1645 (CO) cm^{-1} .

Found: C, 70.9%; H, 4.6%; N, 17.7%; M^+ , 237.

Calc. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$: C, 70.9%; H, 4.7%; N, 17.7%; M , 237.

When the N-oxide (270a) was heated under reflux with phenyl isocyanate in dry xylene for 4h, there was almost quantitative recovery of the unchanged N-oxide (270a).

The use of equimolar quantities of the N-oxide (270a) and phenyl isocyanate in (a) above gave a lower yield (54%) of the product (271a).

(ii) The solid obtained from the N-oxide (270a) and p-chlorophenyl isocyanate was stirred with 10% aqueous sodium hydroxide (5.0 ml) for 30 min. Filtration of this suspension afforded di-(p-chlorophenyl)urea, (33%) as colourless needles, m.p. 293° (from acetic acid-dimethylformamide) (lit.,¹⁹⁸ 307°), ν_{\max} . 3325 (NH) and 1660 (CO) cm^{-1} . Acidification of the filtrate with dilute sulphuric acid afforded unchanged N-oxide (270a) (50%).

(b) 4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b) (0.002 mol) was heated under reflux with (i) phenyl isocyanate, or (ii) p-chlorophenyl isocyanate, (0.002 mol) in dry xylene (10.0 ml) for 4h. The reaction mixtures were filtered hot to remove small amounts (3-7%) of the starting N-oxide (270b). The filtrate on cooling and scratching afforded the solid product, which was combined with any material recovered by evaporating the mother-liquors, and crystallised to yield:-

(i) 2-(N-Phenylamino)-4-methylquinoxalin-3(4H)-one (271c) as cream needles, (53%), m.p. 187° (from ethanol-acetic acid), ν_{\max} . 3325 (NH) and 1655 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 2.30 - 2.56 (9H, m, Ar-H), and 6.01 (3H, s, CH_3).

Found: C, 71.3%; H, 5.1%; N, 16.8%; M^+ , 251.

$\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$ requires: C, 71.7%; H, 5.2%; N, 16.7%; M, 251.

(ii) 2-(N-p-Chlorophenylamino)-4-methylquinoxalin-3(4H)-one (271d), as cream needles, (56%), m.p. 203° (from ethanol-acetic

acid), ν_{\max} . 3300 (NH), 1650 (CO) and 1610 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 2.30 - 2.58 (8H, m, Ar-H), and 6.01 (3H, s, CH_3).

Found: C, 63.1%; H, 4.2%; N, 14.1%; M^+ , 287, 285.

$\text{C}_{15}\text{H}_{12}\text{ClN}_3\text{O}$ requires: C, 63.0%; H, 4.2%; N, 14.7%; M , 287, 285.

The use of a 10% excess of the isocyanates in (i) and (ii) above did not increase the yield of the products (271c-d).

3.3. Attempted Methylation of 2-(N-Phenylamino)quinoxalin-3(4H)-one (271a).

(a) Attempted methylation of 2-(N-phenylamino)quinoxalin-3(4H)-one (271a) to 2-(N-phenylamino)-4-methylquinoxalin-3(4H)-one (271c) by shaking with dimethyl sulphate and 10% aqueous sodium hydroxide, as previously described, resulted in recovery (80%) of the starting material.

(b) Attempted methylation of 2-(N-phenylamino)quinoxalin-3(4H)-one (271a) by heating under reflux in anhydrous acetone for 4h with dimethyl sulphate and anhydrous potassium carbonate, as previously described, afforded a purple gummy material which was not characterised.

3.4. Attempted Acetylation of the 2(N-Phenylamino)quinoxalin-3(4H)-ones (271a) and (271c).

Attempted acetylation of the 2(N-phenylamino)quinoxalin-3(4H)-ones (271a) and (271c) by heating (a) briefly or (b) under reflux for 3h, with acetic anhydride resulted in recovery (70 - 90%) of the starting materials.

3.5. Attempted Synthesis of the 2(N-Phenylamino)quinoxalin-3(4H)-ones (271a) and (271c) from the 2-Cyanoquinoxalin-3(4H)-one 1-N-Oxides (193c-d).

(a) Attempted Reaction of 2-Cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) with Aniline.¹⁷⁰

(i) 2-Cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) (0.002 mol) was heated under reflux with aniline (0.003 mol) in dry xylene (15.0 ml) for 4h. The solid obtained by hot filtration was combined with solid material obtained by diluting the filtrate with light petroleum and crystallised to yield the starting N-oxide (193c) (quantitative).

(ii) 2-Cyanoquinoxalin-3(4H)-one 1-N-oxide (193c) (0.002 mol) was heated under reflux with aniline (0.003 mol) in dimethylformamide (5.0 ml) for 4h. The diluted reaction mixture was extracted with chloroform to give an intractable gum.

[Ahmad¹⁷⁰ reported that heating of 2-cyanoquinoxalin-3(4H)-one (193c) with aniline and dilution of the reaction mixture with light petroleum gave the compound (271a) in 90% yield.]

(b) Attempted Reaction of 2-Cyano-4-methylquinoxalin-3(4H)-one 1-N-Oxide (193d) with Aniline.

(i) 2-Cyano-4-methylquinoxalin-3(4H)-one 1-N-oxide (193d) (0.0025 mol) was heated under reflux with aniline (0.005 mol, 5.0 ml) for 4h. The resulting dark solution was diluted with light petroleum affording an intractable dark gum.

(ii) 2-Cyano-4-methylquinoxalin-3(4H)-one 1-N-oxide (193d) (0.002 mol) was heated under reflux with aniline (0.003 mol) in dimethylformamide (5.0 ml) for 4h. Dilution of the reaction mixture with water afforded an amorphous brown solid

(0.3 g) which could not be characterised. However the i.r. spectrum (ν_{max} . 2300 and 1675 cm^{-1}) of this material was not in accord with that expected for 2-(N-phenylamino)-4-methylquinoxalin-3(4H)-one (271c).

3.6. Reaction of 2-Chloro-4-methylquinoxalin-3(4H)-one (273) with Amines.

(a) (i) N-Methyl-o-phenylenediamine.¹⁷¹

N-Methyl-o-nitroaniline was hydrogenated¹⁷¹ over 10% palladium on charcoal in ethanol to give N-methyl-o-phenylenediamine as a dark gum which was used without further purification.

(ii) 2-Hydroxy-4-methylquinoxalin-3(4H)-one (272).

Condensation¹⁷¹ of N-methyl-o-phenylenediamine with diethyl oxalate afforded compound (272), (74%), m.p. 285° (lit.,¹⁷¹ 287°).

(iii) 2-Chloro-4-methylquinoxalin-3(4H)-one (273).

Treatment¹⁷¹ of compound (272) with phosphoryl chloride afforded compound (273), (17%), m.p. 130° (lit.,¹⁷¹ 131°).

(b) 2-Chloro-4-methylquinoxalin-3(4H)-one (273) (0.002 mol) was heated under reflux with the amine (0.004 mol) in dry xylene (20.0 ml) for 4-7h. The reaction mixture was cooled and the precipitate was collected and washed with water to remove the amine hydrochloride (identified by its i.r. spectrum). The insoluble solid was combined with material obtained by evaporating the xylene mother liquors and crystallised from ethanol-acetic acid to give the respective products.

(i) 2-(N-Phenylamino)-4-methylquinoxalin-3(4H)-one (271c).

Heating under reflux for 7h with aniline afforded compound (271c) in quantitative yield, m.p. 185° , identical (mixed m.p. and i.r. spectrum) with a sample prepared from 4-methylquinoxalin-3(4H)-one 1-N-oxide (270b) and phenyl isocyanate, as described above.

(ii) 2-(N-p-Chlorophenylamino)-4-methylquinoxalin-3(4H)-one (271d).

Heating under reflux for 4h with p-chloroaniline afforded compound (271d), (91%), m.p. 203° , identical (mixed m.p. and i.r. spectrum) with a sample prepared from 4-methylquinoxalin-3(4H)-one 1-N-oxide (270b) and p-chlorophenyl isocyanate, as described above.

(iii) 2-N-Benzylamino-4-methylquinoxalin-3(4H)-one (274).

Heating under reflux for 4h with benzylamine afforded compound (274) as colourless needles, (85%), m.p. 209° (from ethanol-acetic acid), ν_{\max} . 3350 (NH) and 1650 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.70 (1H, t, NH), 2.38 (4H, m, Ar-H), 2.57 (5H, s, Ar-H), 5.20 (2H, d, J 6.0 Hz, CH_2), and 6.08 (3H, s, CH_3).

Found: C, 72.4%; H, 5.6%; N, 16.0%.

$\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}$ requires: C, 72.4%; H, 5.7%; N, 15.8%.

(iv) 2-Diethylamino-4-methylquinoxalin-3(4H)-one (275).

Heating under reflux for 4h with diethylamine afforded an insoluble residue after washing with water (see above) identical (mixed m.p. and i.r. spectrum) with 2-hydroxy-4-methylquinoxalin-3(4H)-one (272) (4%). Evaporation of the xylene mother-liquors gave a gum which was extracted into

chloroform. The extract was washed with saturated aqueous sodium bicarbonate, dried (MgSO_4) and evaporated to give compound (275) as an oil, (70%), $\nu_{\text{max.}}$ 1660 cm^{-1} , τ (CDCl_3) 2.54-3.00 (4H, m, Ar-H), 6.25 (4H, q, J 7.0 Hz, CH_2), 6.47 (3H, s, N- CH_3), and 8.76 (6H, t, J 7.0 Hz, $\text{CH}_2\text{-CH}_3$), which was characterised as its picrate, yellow rhombic plates, m.p. 198° (from ethanol), $\nu_{\text{max.}}$ 1680 and 1640 cm^{-1} .

Found: C, 49.9%; H, 4.2%; N, 18.4%.

$\text{C}_{19}\text{H}_{20}\text{N}_6\text{O}_8$ requires: C, 49.6%; H, 4.4%; N, 18.3%.

(v) Heating under reflux for 9h with ethyl carbamate afforded quantitative recovery of the starting material (273).

3.7. Attempted Reaction of the Quinoxalin-3(4H)-one 1-N-Oxides (270a-b) with Methyl Isocyanate.

(a) Quinoxalin-3(4H)-one 1-N-oxide (270a) (0.005 mol) was heated under reflux for 4h with methyl isocyanate (0.005 mol) in dry xylene (30.0 ml), and was recovered unchanged (97%), by filtration of the reaction mixture.

(b) 4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b) (0.005 mol) was heated under reflux for (i) 4h, and (ii) 96h, with methyl isocyanate (0.005 mol) in dry xylene (30.0 ml). The material obtained by filtration was combined with the solid obtained by evaporating the xylene and triturating the residual gummy solid with ether, to give the starting N-oxide [(i) 91%; (ii) 85%].

3.8. Attempted Reaction of 4-Methylquinoxalin-3(4H)-one 1-N-Oxide (270b) with Carbon Disulphide.

(a) 4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b) (0.002 mol)

was heated under reflux for 4h with carbon disulphide (0.002 mol) in dry xylene (10.0 ml). Filtration of the reaction mixture afforded a solid which was combined with solid material obtained by evaporating the mother-liquors to give the starting N-oxide (75%).

(b) 4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b) (0.002 mol) was heated under reflux for 4h with carbon disulphide (0.004 mol) in dimethylformamide (5.0 ml). Dilution of the reaction mixture with water and chloroform extraction afforded the starting N-oxide (67%).

3.9. Attempted Reaction of 4-Methylquinoxalin-3(4H)-one 1-N-Oxide (270b) with N,N-Dimethyl-p-nitrosoaniline.

4-Methylquinoxalin-3(4H)-one 1-N-oxide (270b) (0.0025 mol) was heated under reflux for 4h with N,N-dimethyl-p-nitrosoaniline (0.0025 mol) in dry xylene (15.0 ml). Filtration of the reaction mixture afforded unchanged starting N-oxide (67%). Evaporation of the filtrate afforded a dark gum which could not be solidified. The gum was extracted into chloroform and washed with 10% aqueous sodium hydroxide. Acidification of the aqueous phase afforded no precipitate.

3.10. Reaction of Quinoxalin-3(4H)-one 1-N-Oxides (270a-b) with Benzyne.

Solutions of the quinoxalin-3(4H)-one 1-N-oxides (270a-b) (0.002 mol) in 1,2-dimethoxyethane (10.0 ml) were heated under reflux and treated dropwise with solutions of amyl nitrite (0.8 ml) in 1,2-dimethoxyethane (4.0 ml) and anthranilic acid (1.0 g) in 1,2-dimethoxyethane (4.0 ml).

Heating was continued for 1h and the products were isolated as described below.

(i) 2-(2'-Hydroxyphenyl)quinoxalin-3(4H)-one (287a).

The yellow-brown suspension (see above) was cooled and the yellow solid was collected and combined with material obtained by evaporating the filtrate under reduced pressure and triturating the brown residue with acetone to give the compound (287a) as yellow needles, (95%), m.p. 307° (from acetic acid-water), ν_{\max} . 1670 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.76 (1H, dd, J_{O} 8.5 Hz, J_{m} 1.5 Hz, H-6'), 1.80-2.30 (5H, m, Ar-H), and 2.60-2.74 (2H, m, Ar-H).

Found: C, 70.1%; H, 4.1%; N, 11.7%; M^+ , 238.

$\text{C}_{14}\text{H}_{10}\text{N}_2\text{O}_2$ requires: C, 70.6%; H, 4.2%; N, 11.8%; M, 238.

(ii) 2-(2'-Hydroxyphenyl)-4-methylquinoxalin-3(4H)-one (287b).

The reaction mixture (see above) was cooled and evaporated under reduced pressure giving a dark gum which on trituration with ether afforded compound (287b) in quantitative yield, m.p. 195° , identical (mixed m.p., i.r. and ^1H n.m.r. spectra) with a sample obtained by methylation of compound (287a). 2-(2'-Hydroxyphenyl)quinoxalin-3(4H)-one (287a) (0.25 g) was heated under reflux in anhydrous acetone (25.0 ml) with anhydrous potassium carbonate (1.0 g). Dimethyl sulphate (1.0 ml) was added dropwise and heating was continued for 8h. The reaction mixture was evaporated under reduced pressure, the residue was treated with water and the solid was collected and crystallised to yield compound (287b) as yellow needles, (0.25 g, 94%), m.p. 212° (from ethanol-acetic acid) ν_{\max} . 1640 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.17 (1H, dd, J_{O} 8.5 Hz, J_{m} 1.5 Hz,

H-6'), 1.90-2.32 (5H, m, Ar-H), 2.60-2.80 (2H, m, Ar-H), and 5.91 (3H, s, N-CH₃).

Found: C, 71.6%; H, 4.7%; N, 10.7%; M⁺, 252.

C₁₅H₁₂N₂O₂ requires: C, 71.4%; H, 4.8%; N, 11.1%; M, 252.

3.11. 2-(2'-Methoxyphenyl)-4-methylquinoxalin-3(4H)-one (287d).

(a) 2-(2'-Hydroxyphenyl)-4-methylquinoxalin-3(4H)-one (287b) (0.1 g) was suspended in 10% aqueous sodium hydroxide (2.0 ml) and dimethyl sulphate (0.25 ml) was added dropwise with vigorous shaking. The reaction mixture was heated on a boiling water bath for 15 min, then cooled and the yellow solid was collected (0.09 g, 85%), m.p. 153°, identical (mixed m.p. and i.r. spectrum) with a sample prepared by unambiguous synthesis, as described below.

(b)(i) 2-Methoxyphenylacetyl chloride.

2-Methoxyphenylacetic acid (0.07 mol) was heated with thionyl chloride (0.14 mol) on a water bath at 80° for 15 min giving a yellow solution. Heating for a further 30 min to ensure complete reaction caused a red colour to develop. The excess of thionyl chloride was removed by distillation leaving the acid chloride as a red liquid, (quantitative yield),
 $\nu_{\text{max.}} 1800 \text{ (CO) cm}^{-1}$.

(ii) o-(2'-Methoxyphenyl)-2-nitroacetanilide (288).

A solution of o-nitroaniline (0.14 mol) and 2-methoxyphenylacetyl chloride (0.14 mol) in dry benzene (50.0 ml) was heated on a boiling water bath for 2h giving a red solution. Evaporation under reduced pressure afforded a viscous gum which slowly solidified on trituration with ether giving compound (288)

as a yellow solid, (92%), m.p. 51° (from light petroleum-benzene), ν_{\max} . 3350 (NH) and 1705 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.50-3.00 (8H, m, Ar-H), 6.00 (2H, s, CH_2) and 6.08 (3H, s, OCH_3).

Found: C, 62.8%; H, 4.8%; N, 10.0%.

$\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_4$ requires: C, 62.9%; H, 4.9%; N, 9.8%.

(iii) 2-(2'-Methoxyphenyl)quinoxalin-3(4H)-one 1-N-oxide (289a).

α -(2'-Methoxyphenyl)-2-nitroacetanilide (288) (15.0 g) was dissolved in pyridine (75.0 ml) and 20% aqueous potassium hydroxide (150 ml) was added. The reaction mixture was heated on a boiling water bath for 1h with vigorous stirring, then cooled and diluted with water (500 ml). The red oil which separated was recovered in chloroform to afford o-nitroaniline. The aqueous layer was acidified with dilute hydrochloric acid but no precipitate was obtained. The acidic solution was extracted with chloroform, and the extract was washed with dilute sulphuric acid to remove pyridine and then with saturated sodium bicarbonate solution. The sodium bicarbonate washings were acidified giving a creamy solid (5.1 g, 58%), identical (mixed m.p. and i.r. spectrum) with 2-methoxyphenyl-acetic acid.

Evaporation of the chloroform extract gave a gum, which on trituration with acetone afforded compound (289a) as pale yellow hexagonal platelets, (17%), m.p. 267° (from ethanol), ν_{\max} . 1650 (CO) and 1620 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.32 (1H, dd, J_0 8.5 Hz, H-6'), 2.00-2.86 (7H, m, Ar-H) and 6.10 (3H, s, OCH_3).

Found: C, 67.2%; H, 4.3%; N, 10.6%; M^+ , 268.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_3$ requires: C, 67.2%; H, 4.5%; N, 10.4%; M, 268.

(iv) 2-(2'-Methoxyphenyl)-4-methylquinoxalin-3(4H)-one 1-N-oxide (289b).

2-(2'-Methoxyphenyl)quinoxalin-3(4H)-one 1-N-oxide (289a) (1.5 g) was suspended in 10% aqueous sodium hydroxide (15.0 ml) and dimethyl sulphate (2.5 ml) was added in portions with vigorous shaking. Initially a solution was obtained but was followed by the precipitation of a yellow solid. The reaction mixture was heated on a boiling water bath for 15 min, cooled, and the yellow solid was filtered off giving compound (289b) as pale yellow plates, (62%), m.p. 206° (from ethanol), ν_{\max} . 1660 (CO) and 1620 cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.34 (1H, dd, J_{O} 8.5 Hz, H-6'), 2.00-2.86 (7H, m, Ar-H), 5.96 (3H, s, NCH_3) and 6.10 (3H, s, OCH_3).

Found: C, 68.1%; H, 5.0%; N, 10.3%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_3$ requires: C, 68.1%; H, 5.0%; N, 9.9%.

(v) 2-(2'-Methoxyphenyl)-4-methylquinoxalin-3(4H)-one (287d)

2-(2'-Methoxyphenyl)-4-methylquinoxalin-3(4H)-one 1-N-oxide (289b) (0.5 g) was heated under reflux with sodium dithionite (1.0 g) (added in two portions, the second portion after 1h) in 70% aqueous ethanol (25.0 ml) for 2h. Filtration and concentration of the reaction mixture yielded a solid which was washed with water to give compound (287d) as pale yellow plates, (80%), m.p. 171° (from ethanol), ν_{\max} . 1660 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 1.40 (1H, dd, J_{O} 8.0 Hz, J_{m} 1.5 Hz, H-6), 1.84 - 2.30 (5H, m, Ar-H), 2.60-2.75 (2H, m, Ar-H), 5.84 (3H, s, OCH_3), and 5.90 (3H, s, NCH_3).

Found: C, 71.9%; H, 5.2%; N, 10.9%.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2$ requires: C, 72.2%; H, 5.3%; N, 10.5%.

This product was identical (mixed m.p. and i.r. spectrum) with a sample obtained by complete methylation of the products (287a) and (287b) obtained by the reaction of benzyne with quinoxalin-3(4H)-one 1-N-oxides (270a-b).

(vi) 2-(2'-Methoxyphenyl)quinoxalin-3(4H)-one (287c)

Sodium dithionite reduction of 2-(2'-Methoxyphenyl)quinoxalin-3(4H)-one 1-N-oxide (289a), as described above, afforded compound (287c) as pale yellow rhombic plates, (80%), m.p. 236° (from ethanol), ν_{\max} . 1660 (CO) cm^{-1} , τ ($\text{CF}_3\text{CO}_2\text{H}$) 0.98 (1H, dd, J_0 8.5 Hz, H-6'), 1.90-2.30 (5H, m, Ar-H), 2.52-2.68 (2H, m, Ar-H), and 5.73 (3H, s, OCH_3).

Found: C, 71.3%; H, 4.7%; N, 11.3%.

$\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$ requires: C, 71.4%; H, 4.8%; N, 11.1%.

3.12. Reaction of Sodium Ethyl Benzoylpyruvate with o-Phenylenediamines.

Sodium ethyl benzoylpyruvate (0.1 mol) in water (45.0 ml) was added to a solution of the o-phenylenediamine (0.15 mol) in ethanol (75.0 ml). Glacial acetic acid (30.0 ml) was added and the reaction mixture was warmed on a boiling water bath for 30 min. On cooling the 2(1H)-benzoylmethylenequinoxalin-3(4H)-ones (294a-b) were collected. Working up the mother liquor gave no further material.

(i) 2(1H)-Benzoylmethylenequinoxalin-3(4H)-one (294a) was obtained as a yellow solid, (70%), m.p. 275° (from glacial acetic acid), ν_{\max} . 1690 and 1620 (CO) cm^{-1} , τ (DMSO-d_6) 2.04 (2H, m, Ar-H), 2.50 (4H, m, Ar-H), 2.86 (3H, m, Ar-H) and 3.18 (1H, s, =CH).

Found: C, 72.8%; H, 4.9%; N, 10.6%.

C₁₆H₁₂N₂O₂ requires: C, 72.7%; H, 4.6%; N, 10.6%.

(ii) 2(1H)-Benzoylmethylene-4-methylquinoxalin-3(4H)-one (294b) was obtained as a yellow solid, (71%), m.p. 186° (from benzene), ν_{\max} . 1660 and 1615 (CO) cm⁻¹, τ (CDCl₃) 2.00 (2H, m, Ar-H), 2.56 (3H, m, Ar-H), 2.84 (4H, m, Ar-H), 3.00 (1H, s, olefinic CH) and 6.38 (3H, s, CH₃).

Found: C, 73.1%; H, 5.0%; N, 10.2%.

C₁₇H₁₄N₂O₂ requires: C, 73.4%; H, 5.1%; N, 10.1%.

3.13. Reaction of the Quinoxalin-3(4H)-one 1-N-Oxides (270a-b) with Dibenzoylmethane.

A suspension of the quinoxalin-3(4H)-one 1-N-oxide (270) (0.01 mol) and dibenzoylmethane (0.01 mol) in ethanol (75.0 ml) was heated under reflux with piperidine (3.0 ml) for 30 min giving a red solution. The products were isolated as described below.

(i) 2-Phenacylquinoxalin-3(4H)-one (293a).

The reaction mixture was cooled and the orange precipitate was collected and combined with material obtained by evaporating the ethanol and washing the residual orange solid with water and saturated aqueous sodium bicarbonate, to afford crude 2-phenacylquinoxalin-3(4H)-one (293a) (94%). Hot ethanol leaching left an orange residue of 2(1H)-benzoylmethylenequinoxalin-3(4H)-one (294a), (2%), identical (mixed m.p. and i.r. spectrum) with an authentic sample (see before). 2-Phenacylquinoxalin-3(4H)-one (293a) crystallised from the ethanol mother liquor as white needles, m.p. 214° (from ethanol),

ν_{\max} . 1700 (CO) and 1620 cm^{-1} , τ (DMSOD₆) 1.92-3.11 (9H, m, Ar-H) and 5.84 (2H, d, J 4.0 Hz, CH₂).

Found: C, 72.8%; H, 4.7%; N, 10.7%.

C₁₆H₁₂N₂O₂ requires: C, 72.7%; H, 4.6%; N, 10.6%.

(ii) 2(1H)-Benzoylmethylene-4-methylquinoxalin-3(4H)-one (294b).

Evaporation of the reaction mixture under reduced pressure gave a gelatinous solid which was extracted into chloroform and washed with water. Acidification of the aqueous layer afforded benzoic acid, identical (mixed m.p. and i.r. spectrum) with an authentic sample. The chloroform extract was washed with dilute sulphuric acid, dried (MgSO₄) and evaporated to afford an oil. Trituration with benzene yielded 2(1H)-benzoylmethylene-4-methylquinoxalin-3(4H)-one (294b) (36%), identical (mixed m.p. and i.r. spectrum) with a sample obtained as described above.

3.14. ¹H n.m.r. Spectra of the Quinoxalin-3(4H)-ones (295).

(a) 2-Acetylmethylenequinoxalin-3(4H)-one (295a) had τ (DMSOD₆) 2.68 (1H, m, Ar-H), 2.92 (3H, m, Ar-H), 3.95 (1H, s, olefinic CH) and 7.84 (3H, s, CH₃); τ (CF₃CO₂H) 2.20-2.50 (4H, m, Ar-H), 2.44 (1H, s, olefinic CH) and 7.40 (3H, s, CH₃).

(b) Ethyl [quinoxalin-3(4H)-onyl-3]acetate (295b) had τ (DMSOD₆) 2.60-3.00 (4H, m, Ar-H), 4.52 (1H, s, olefinic CH), 5.86 (2H, q, J 7.0 Hz, CH₂) and 8.78 (3H, t, J 7.0 Hz, CH₃); τ (CF₃CO₂H) 1.80-2.32 (4H, m, Ar-H), 5.52 (2H, s, CH₂), 5.56 (2H, q, J 7.0 Hz, CH₂CH₃) and 8.62 (3H, t, J 7.0 Hz, CH₃).

3.15. Alkaline Hydrolysis of the Tautomers (293a) and (294a).

The tautomeric ketones (i) (293a) and (ii) (294a), (0.001 mol) were heated under reflux in 20% aqueous potassium hydroxide (10.0 ml) for 1h. The reaction mixture was acidified, extracted with chloroform and the chloroform extract washed with saturated aqueous sodium bicarbonate. The aqueous layer was acidified to afford benzoic acid, identical (mixed m.p. and i.r. spectrum) with an authentic sample. The chloroform extract afforded 2-methylquinoxalin-3(4H)-one (296) [(i) 67% and (ii) quantitative] identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample.¹⁹⁹

3.16. Chromic Acid Oxidation of the Tautomers (293a) and (294a).

The tautomeric ketones (i) (293a) and (ii) (294a), (0.001 mol) were heated in 70% (v/v) aqueous acetic acid (30.0 ml) on a boiling water bath with chromium trioxide (0.53 g) for 1h. The reaction mixture was left overnight, concentrated by partial evaporation and diluted with water, to afford quinoxalin-2,3(1H,4H)-dione (297), [(i) 25% and (ii) 25%], identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample.²⁰⁰ Extraction of the mother liquors with chloroform afforded benzoic acid, identical (mixed m.p. and i.r. spectrum) with an authentic sample.

3.17. Methylation of the Tautomers (293a) and (294a).

(a) The yellow ketone (294a) (0.0025 mol) was dissolved in 4% aqueous sodium hydroxide (10.0 ml) and warmed to ensure salt

formation. Methanol (10.0 ml) and methyl iodide (0.3 ml) were added and the reaction mixture was shaken for 5h. Evaporation of the methanol and filtration afforded a yellow solid which on leaching with hot benzene yielded the unchanged ketone (294a) (33%). The benzene mother liquors afforded the N-methyl ketone (294b), (42%), identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained as described above.

Attempted methylation of (294a) by heating under reflux in acetone with potassium carbonate and methyl iodide afforded the N-methyl ketone (294b) in < 1% yield.

(b) Attempted methylation of the colourless ketone (293a) by heating under reflux in anhydrous acetone with anhydrous potassium carbonate and methyl iodide resulted in recovery (87%) of unchanged starting material.

3.18. Attempted Interconversion of the Tautomers (293a) and (294a)

The colourless ketone (293a) (0.1 g) was suspended in 10% aqueous sodium hydroxide and heated to obtain solution. Acidification on cooling afforded quantitative recovery of unchanged colourless ketone (293a).

3.19. Reaction of the Quinoxalin-3(4H)-one 1-N-Oxides (270a-b) with Phenylacetylene.

The quinoxalin-3(4H)-one 1-N-oxides (270a-b) (0.01 mol) were heated under reflux in dry xylene (50.0 ml) with phenylacetylene (1.1 ml) for 3h. The products were isolated as described below.

(i) Filtration of the reaction mixture (see above) from quinoxalin-3(4H)-one 1-N-oxide (270a) afforded compound Y as a pale yellow solid, (41%), m.p. 261° (from glacial acetic acid, ν_{\max} . 3400 (NH) and 1700 (CO) cm^{-1} , τ (DMSO- d_6) 1.96 (4H, m, Ar-H), 2.30 (6H, m, Ar-H), 3.05-3.36 (8H, m, Ar-H), 4.24 (2H, s) and 5.14 (2H, s).

Found: C, 68.5%; H, 4.9%; N, 9.5%; M^+ , 528.

$C_{32}H_{24}N_4O_4$ requires: C, 72.7%; H, 4.6%; N, 10.6%; M, 528.

Evaporation of the mother liquors and trituration of the residual glass with methanol-ether afforded a yellow solid Z (1.1 g, 50%), m.p. 266° (from ethanol), ν_{\max} . 1680 (CO) cm^{-1} , τ (CDCl $_3$) 2.00-3.20 (m, Ar-H).

Found: C, 73.7%; H, 4.4%; N, 10.8%; M^+ , 260.

$C_{16}H_8N_2O_2$ requires: C, 73.8%; H, 3.1%; N, 10.8%; M, 260.

(ii) Filtration of the reaction mixture (see above) from 4-methylquinoxalin-3(4H)-one 1-N-oxide (270b) afforded compound X as a colourless solid (59%), m.p. 285° (from dimethylformamide), ν_{\max} . 1665 (CO) cm^{-1} , τ (CF $_3$ CO $_2$ H) 1.98 - 3.44 (18H, m, Ar-H), 3.94 (2H, s), 4.52 (2H, s) and 6.40 (6H, s, 2-CH $_3$).

Found: C, 71.6%; H, 4.9%; N, 10.5%; M^+ , 556.

$C_{34}H_{28}N_4O_4$ requires: C, 73.4%; H, 5.1%; N, 10.1%; M, 556.

Evaporation of the mother liquors afforded a red gum; T.L.C. on alumina in benzene-ether showed three main spots which did not separate cleanly on column chromatography. The red gum would not solidify on trituration with organic solvents and was not further investigated.

3.20. Attempted Characterisation of Compound X.

(a) Reduction.

- (i) Heating under reflux with sodium dithionite in glacial acetic acid afforded unchanged starting material (90%).
- (ii) Attempted catalytic hydrogenation over palladium-charcoal afforded unchanged starting material (44%) after extracting the catalyst with boiling dimethylsulphoxide.
- (iii) Heating under reflux in glacial acetic acid with iron filings afforded unchanged starting material (55%).

(b) Acid Hydrolysis.

Compound X (0.15 g) was suspended in glacial acetic acid (3.0 ml) and heated under reflux with 20% (w/v) aqueous sulphuric acid (1.5 ml) for 3h. Filtration afforded unchanged starting material (86%).

(c) Alkaline Hydrolysis.

(i) Compound X (1.0 g) was suspended in ethanol (50.0 ml) and heated under reflux for 1h with 10% aqueous sodium hydroxide (25.0 ml). Hot filtration of the reaction mixture afforded unchanged starting material, (0.45 g, 45%). Concentration of the filtrate gave a yellow solid (0.6 g) which was washed with water. This solid was mainly starting material and the small amount of other material present could not be isolated by fractional crystallisation.

(ii) Compound X (0.001 mol) was heated under reflux in trigol (2.0 ml) and water (2 drops) with potassium hydroxide (one pellet) for 7 min. The dark red solution was diluted with water. Chloroform extraction gave a dark oil, T.L.C. on

silica in benzene-ether showed six components. Acidification of the aqueous layer and chloroform extraction afforded a dark oil, T.L.C. on silica in benzene-ether showed five components.

(d) Chromic Acid Oxidation.

Compound X (1.0 g) was suspended in 70% (v/v) aqueous acetic acid (75.0 ml) and heated with chromium trioxide (2.0 g) on a boiling water-bath for 1h. Hot filtration of the reaction mixture afforded unchanged starting material (0.37 g, 37%). The filtrate was concentrated and diluted with water and the pale solid was collected, (0.43 g), m.p. 250° (from acetic acid-dimethylformamide), ν_{\max} . 1680 (CO) cm^{-1} .

Found: C, 69.1%; H, 4.4%; N, 10.6%; M^+ , 410 or 362.

3.21. Chromic Acid Oxidation of Compound Z.

A solution of compound Z (0.25 g) in 70% (v/v) aqueous acetic acid (7.0 ml) was heated with chromium trioxide (0.5 g) on a boiling water bath for 35 min. The reaction mixture was evaporated and the residual solid was washed with water to yield quinoxalin-2,3(1H,4H)-dione (297) (0.09 g) identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample.²⁰⁰ Chloroform extraction of the mother-liquors afforded benzoic acid (0.04 g), identical (mixed m.p., and i.r. spectrum) with an authentic sample.

SECTION FOUR

4.1. Preparation of Oximino-carbonyl compounds (303).

The following oximes were prepared by nitrosation of the corresponding α -methyl (or substituted methyl) ketones, $\nu_{\text{max.}}$ 3400-3150 (OH) and 1670-1645 (CO) cm^{-1} .

(i) 2-Oximino-1-phenylpropan-1-one (303a), (70%), had m.p. 105° (lit.,²⁰¹ 113°), τ (CDCl_3) 2.15-2.80 (5H, m, Ar-H), 5.16 (1H, s br, OH) and 7.90 (3H, s, CH_3).

(ii) 1-Oximino-1-phenylpropan-2-one (303b), (42%), had m.p. $138-145^{\circ}$ (lit.,²⁰² 167°), τ (CDCl_3) 2.64-2.76 (5H, m, Ar-H) and 7.51 (3H, s, CH_3).

(iii) 2-Oximinoacetophenone (303c), (37%), had m.p. $105-110^{\circ}$ (lit.,²⁰³ 128°), τ (CDCl_3) 1.88 (1H, s, H-2), 2.00-2.66 (5H, m, Ar-H) and 3.02 (1H, s br, OH).

(iv) 1-Oximinopropan-2-one (303d), (75%), had m.p. 61° (lit.,²⁰⁴ 69°), τ (CDCl_3) 2.40 (1H, s, H-1) and 7.57 (3H, s, CH_3).

(v) 2-Cyano-2-oximinoacetophenone (303e), (93%), had m.p. 119° (lit.,²⁰⁵ 119°).

(vi) Ethyl 2-oximino-3-oxo-3-methylpropionate (303f) had τ (CDCl_3) 5.68 (2H, q, J 7.0 Hz, CH_2), 7.67 (3H, s, CH_3) and 8.66 (3H, t, J 7.0 Hz, CH_2CH_3).

(vii) Ethyl 2-oximino-3-oxo-3-phenylpropionate (303h), (quantitative), had m.p. 116° (lit.,²⁰⁶ 121°), τ (CDCl_3) 0.60 (1H, s br, OH), 2.10-2.62 (5H, m, Ar-H), 5.75 (2H, q, J 7.0 Hz, CH_2) and 8.81 (3H, t, J 7.0 Hz, CH_3).

(viii) 3-Oximinopentan-2,4-dione (303j), (65%), had m.p. 75° (lit.,²⁰⁷ 75°), τ (CDCl_3) 7.59 (6H, s, CH_3).

4.2. Preparation of Oxazole 3-N-Oxides (301), (305) and (308).

The oxazole 3-N-oxides (301), (305) and (308) were prepared according to the method of Dilthey and Friedrichsen.¹⁸² A solution or suspension of the oximino-compound (0.1 mol) and the aldehyde (0.1 mol) in glacial acetic acid (40.0-100 ml) was saturated with dry hydrogen chloride gas. The resulting yellow to red solution was left stoppered at room temperature for 16-24 h then diluted with ether (100 ml) precipitating the oxazole 3-N-oxide hydrochloride (300), (304) or (307), ν_{\max} . 2300-1800 br (NH^+) and 1685-1665 cm^{-1} , ^1H n.m.r. spectra, Table 7. The hydrochloride was stirred in dilute ammonium hydroxide (75.0 ml) for 2h and the oxazole 3-N-oxide (301), (305) or (308) was collected and dried in vacuo over phosphorus pentoxide, ν_{\max} . 1680 cm^{-1} , ^1H n.m.r. spectra, Table 7.

(i) 4,5-Dimethyl-2-phenyloxazole 3-N-oxide (301a), (69%), had m.p. 100° (lit.,¹⁸² 104°).

(ii) 2-(p-Chlorophenyl)-4,5-dimethyloxazole 3-N-oxide (301b) was obtained as white platelets, (69%), m.p. 129° (from benzene-light petroleum).

Found: C, 59.1%; H, 4.3%; N, 6.1%.

$\text{C}_{11}\text{H}_{10}\text{ClNO}_2$ requires: C, 59.1%; H, 4.5%; N, 6.3%.

(iii) 4,5-Dimethyl-2-(p-methoxyphenyl)oxazole 3-N-oxide (301c), (80%), had m.p. 140° (lit.,¹⁸² 141°).

(iv) 4,5-Dimethyl-2-(p-tolyl)oxazole 3-N-oxide (301d) was obtained as white needles, (75%), m.p. 136° (from benzene-light petroleum).

Found: C, 68.2%; H, 6.6%; N, 7.1%.

C₁₂H₁₃NO₂ requires: C, 70.9%; H, 6.5%; N, 6.9%.

(v) 4,5-Dimethyl-2-(o-hydroxyphenyl)oxazole 3-N-oxide (301e)
(64%), had m.p. 105° (lit.,¹⁸² 106°).

(vi) 4,5-Dimethyl-2-(m-nitrophenyl)oxazole 3-N-oxide (301f)
was obtained (75%), m.p. 150° (lit.,¹⁸² 160°) by concentrating
the reaction mixture and diluting it with water.

(vii) 4,5-Dimethyl-2-(p-nitrophenyl)oxazole 3-N-oxide (301g)
was obtained (57%), m.p. 192° (lit.,¹⁸² 200°) by diluting the
reaction mixture with water.

(viii) 4,5-Dimethyl-2-(p-N,N-dimethylaminophenyl)oxazole
3-N-oxide (301h).

The hydrochloride (300h) was obtained by evaporating
the reaction mixture and triturating with water. Careful
trituration and stirring with dilute ammonium hydroxide for
4h afforded the crude oxazole 3-N-oxide (301h). Trace
amounts of p-N,N-dimethylaminobenzaldehyde were removed by
crystallisation yielding the pure N-oxide as a tan solid,
(60%), m.p. 162° (from benzene).

Found: C, 67.4%; H, 6.8%; N, 11.5%.

C₁₃H₁₆N₂O₂ requires: C, 67.2%; H, 6.9%; N, 12.1%.

(ix) 2,4,5-Trimethyloxazole 3-N-oxide hydrochloride (300j).

Evaporation of the reaction mixture and trituration of
the residual oil with ether afforded the hydrochloride (300j)
as a pale brown solid (88%), unstable to crystallisation,
¹H n.m.r. spectrum (see Table 7). Treatment with dilute

ammonium hydroxide, as described above, failed to afford a solid. A solution of the hydrochloride in the minimum of water was triturated with solid sodium acetate but no precipitate formed. A solution of the hydrochloride in the minimum of chloroform was shaken with solid sodium bicarbonate and filtered. Evaporation of the chloroform afforded an oil, shown by T.L.C. and by its ^1H n.m.r. spectrum to be a mixture of several components. The hydrochloride (300j) did not give a picrate or a boron trifluoride adduct (see below).

(x) 2,5-Diphenyl-4-methyloxazole 3-N-oxide (305a), (75%), had m.p. 151° (lit.,¹⁸² 153°).

(xi) As reported by Dilthey and Friedrichsen,¹⁸² attempted condensation of 1-oximino-1-phenylpropan-2-one (303b) with benzaldehyde, as described above, gave on work-up a dark intractable oil which resisted further characterisation.

(xii) 2,5-Diphenyloxazole 3-N-oxide (305c), (4%), was identical (i.r. spectrum) with the product obtained by dithionite reduction of the boron trifluoride adduct (306c) (see below). There was insufficient material to characterise and attempted crystallisation from benzene caused decomposition.

(xiii) 5-Methyl-2-phenyloxazole 3-N-oxide hydrochloride (304d)

The reaction mixture was diluted with ether to afford the hydrochloride (304d) as a hygroscopic pale yellow solid (30%). Attempted liberation of the free N-oxide, as in (ix), was unsuccessful.

(xiv) The reaction mixture from the attempted condensation of 2-cyano-2-oximinoacetophenone (303e) with benzaldehyde was evaporated and extracted with chloroform. After washing with saturated aqueous sodium bisulphite the extract afforded unchanged starting oxime (62%).

(xv) Ethyl 5-methyl-2-phenyloxazole-4-carboxylate 3-N-oxide (305f). Dilution of the reaction mixture (see above) with ether afforded the hydrochloride (304f), (78%), as a hygroscopic white solid, ν_{\max} . 1780-1760 br (NH^+), 1710 (CO) and 1660 cm^{-1} . A solution of the hydrochloride in the minimum of water, triturated with sodium acetate afforded the oxazole 3-N-oxide (305f) as a white solid, ν_{\max} . 1720 (CO) and 1630 cm^{-1} , which almost immediately decomposed to a yellow gum.

Found: C, 62.9%; H, 5.6%; N, 5.5%.

$\text{C}_{13}\text{H}_{13}\text{NO}_4$ requires: C, 63.2%; H, 5.3%; N, 5.7%.

The hydrochloride (304f) (0.015 mol) was warmed with 10% aqueous sodium hydroxide (10.0 ml) for 1 min. The yellow solution was cooled and acidified with dilute sulphuric acid. The white precipitate was collected and crystallised from ethanol to afford 5-methyl-2-phenyloxazole-4-carboxylic acid 3-N-oxide (305g) as white needles, (32%), m.p. 147° (from ethanol), ν_{\max} . 3500 br (OH), 1700 (CO) and 1650 cm^{-1} , τ (CDCl_3) 1.59-1.69 (2H, m, Ar-H), 2.17-2.30 (3H, m, Ar-H) and 7.23 (3H, s, CH_3).

Found: C, 60.6%; H, 4.2%; N, 6.2%; M^+ , 219.

$\text{C}_{11}\text{H}_9\text{NO}_4$ requires: C, 60.3%; H, 4.1%; N, 6.4%; M , 219.

(xvi) The attempted condensation of ethyl 2-oximino-3-oxo-3-

phenylpropionate (303h) with benzaldehyde, as described above, resulted in recovery (86%) of the starting oxime.

(xvii) 4,5-Diphenyl-2-methyloxazole 3-N-oxide (308).

The hydrochloride (307) was obtained by evaporating the reaction mixture, and triturating with ether. Treatment with dilute ammonium hydroxide, as above, afforded the crude N-oxide (308), (93%), which decomposed on attempted crystallisation and would not form a picrate or boron trifluoride adduct. After drying in vacuo over P_2O_5 , the N-oxide (308) decomposed immediately to a dark gum on exposure to air. A solution of this gum in ethanol, treated with cold 10% aqueous sodium hydroxide afforded benzil, identical (mixed m.p. and i.r. spectrum) with an authentic sample.

4.3. Preparation of Oxazole 3-N-Oxide Boron Trifluoride Adducts (302), (306) and (309).

(a) Boron trifluoride-etherate (1.5 ml, slight excess) was added to a solution or suspension of the oximino-compound (0.01 mol) and the aldehyde (0.01 mol) in glacial acetic acid (10.0 ml). The reaction mixture was left stoppered at room temperature for 15-24h. Precipitated solid was collected and combined with material obtained by evaporating the mother liquors and triturating the residual oil with ether or methanol-ether to afford the oxazole 3-N-oxide boron trifluoride adduct (302), (306) or (309), 1H n.m.r. spectra, Table 7.

(i) 4,5-Dimethyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (302a) was obtained as tiny white needles, (81%), m.p. 174° (from glacial acetic acid), ν_{max} . 1680 cm^{-1} .

Found: C, 51.4%; H, 4.3%; N, 5.0%; M⁺, 189.

C₁₁H₁₁BF₃NO₂ requires: C, 51.4%; H, 4.3%; N, 5.4%; M, 257.

(ii) 2,4,5-Trimethyloxazole 3-N-oxide boron trifluoride adduct (302j) was obtained as colourless plates, (59%), m.p. 85° (benzene-light petroleum), $\nu_{\text{max.}}$ 1680 cm⁻¹.

Found: C, 36.8%; H, 4.6%; N, 7.6%.

C₆H₉BF₃NO₂ requires: C, 36.9%; H, 4.6%; N, 7.2%.

(iii) 2,5-Diphenyl-4-methyloxazole 3-N-oxide boron trifluoride adduct (306a) was obtained as white needles, (60%), m.p. 173° (from glacial acetic acid) after drying at 100° to remove acetic acid of crystallisation, $\nu_{\text{max.}}$ 1650 cm⁻¹.

Found: C, 59.6%; H, 4.0%; N, 4.4%.

C₁₆H₁₃BF₃NO₂ requires: C, 60.2%; H, 4.1%; N, 4.4%.

(iv) 2,4-Diphenyl-5-methyloxazole 3-N-oxide boron trifluoride adduct (306b) was obtained after 15h as colourless prisms, (39%), m.p. 196° (from glacial acetic acid), $\nu_{\text{max.}}$ 1665 cm⁻¹.

Found: N, 4.6%.

C₁₆H₁₃BF₃NO₂ requires: N, 4.4%.

(v) 2,5-Diphenyloxazole 3-N-oxide boron trifluoride adduct (306c) was obtained as white needles (34%), m.p. 207° (from glacial acetic acid), $\nu_{\text{max.}}$ 3200 and 1640 cm⁻¹.

Found: C, 59.0%; H, 3.8%; N, 5.0%.

C₁₅H₁₁BF₃NO₂ requires: C, 59.0%; H, 3.6%; N, 4.6%.

(vi) 5-Methyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (306d) was obtained as colourless prisms, (16%), m.p. 158° (from glacial acetic acid), $\nu_{\text{max.}}$ 3200 and 1660 cm⁻¹.

Found: C, 49.3%; H, 3.7%; N, 6.1%.

C₁₀H₉BF₃NO₂ requires: C, 49.4%; H, 3.7%; N, 5.8%.

(vii) 4-Cyano-2,5-diphenyloxazole 3-N-oxide boron trifluoride adduct (306e) was obtained as white needles, (53%), m.p. 165° (from glacial acetic acid), ν_{\max} . 2300 (CN) and 1640 cm⁻¹.

Found: C, 58.6%; H, 3.0%; N, 8.5%.

C₁₆H₁₀BF₃N₂O₂ requires: C, 58.2%; H, 3.0%; N, 8.5%.

(viii) Ethyl 5-methyl-2-phenyloxazole-4-carboxylate 3-N-oxide boron trifluoride adduct (306f) was obtained as white needles, (69%), m.p. 162° (from glacial acetic acid), ν_{\max} . 1740 (CO), 1660 (W) and 1610 cm⁻¹.

Found: C, 49.5%; H, 4.1%; N, 4.6%.

C₁₃H₁₃BF₃NO₄ requires: C, 49.5%; H, 4.1%; N, 4.4%.

(ix) Ethyl 2,5-diphenyloxazole-4-carboxylate 3-N-oxide boron trifluoride adduct (306h).

Application of the method described above afforded a white solid which was washed with saturated aqueous sodium bicarbonate to afford the adduct (306h) as colourless plates, (16%), m.p. 187° (from glacial acetic acid), ν_{\max} . 1725 (CO) and 1620 cm⁻¹.

Found: N, 4.2%.

C₁₈H₁₅BF₃NO₄ requires: N, 3.7%.

Acidification of the bicarbonate washings afforded benzoic acid, (50%, based on benzaldehyde), identical (mixed m.p. and i.r. spectrum) with an authentic sample.

(x) Attempted preparation of 4-acetyl-5-methyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (306j), as above, yielded an intractable oil.

(xi) 4,5-Diphenyl-2-methyloxazole 3-N-oxide boron trifluoride adduct (309) was obtained as cream plates, (70%), m.p. 154° (from glacial acetic acid), ν_{\max} . 1660 cm^{-1} .

Found: C, 60.2%; H, 4.3%; N, 5.0%.

$\text{C}_{16}\text{H}_{13}\text{BF}_3\text{NO}_2$ requires: C, 60.2%; H, 4.1%; N, 4.4%.

(b) Boron trifluoride-etherate (0.75 ml, slight excess) was added to a solution of the oxazole 3-N-oxide (301a), (305a) or (305f) (0.005 mol) in glacial acetic acid (5.0 ml). The reaction mixture was shaken for a few moments, left stoppered at room temperature for 30 min and the precipitated oxazole 3-N-oxide boron trifluoride adduct (302a), (306a) or (306f) was collected and washed with ether. The adducts thus obtained were identical (m.p., mixed m.p. and i.r. spectrum) with the corresponding adduct obtained by method (a) (see above).

(i) 4,5-Dimethyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (302a) was obtained in quantitative yield.

(ii) 2,5-Diphenyl-4-methyloxazole 3-N-oxide boron trifluoride adduct (306a) was obtained in quantitative yield.

(iii) Ethyl 5-methyl-2-phenyloxazole-4-carboxylate 3-N-oxide boron trifluoride adduct (306f), (74%).

4.4. Attempted Conversion of the Oxazole 3-N-Oxide Boron Trifluoride Adducts (302) and (306) into the Corresponding Oxazole 3-N-Oxides (301) and (305).

(a) In Acetonitrile.

A solution of 4,5-dimethyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (302a) (0.2 g) in acetonitrile

(3.0 ml) was left at room temperature for 65h. Evaporation of the solvent afforded quantitative recovery of the adduct (302a).

(b) In Dilute Ammonium Hydroxide.

A suspension of the oxazole 3-N-oxide boron trifluoride adduct (302a), (306a-c) or (306e) (0.001 mol) in dilute ammonium hydroxide (5.0 ml) was stirred at room temperature for 8 - 24h and then filtered.

(i) 4,5-Dimethyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (302a) afforded the N-oxide (301a) (54%), identical (mixed m.p. and i.r. spectrum) with a sample prepared as described above.

(ii) 2,5-Diphenyl-4-methyloxazole 3-N-oxide boron trifluoride adduct (306a) was recovered (80%) unchanged after 8h, but after 24h, afforded the N-oxide (305a) (quantitative), identical (mixed m.p. and i.r. spectrum) with a sample prepared as described above.

(iii) 2,5-Diphenyl-5-methyloxazole 3-N-oxide boron trifluoride adduct (306b) was recovered (80-90%), unchanged after 8h or 24h.

(iv) 2,5-Diphenyloxazole 3-N-oxide boron trifluoride adduct (306c) was recovered (88-90%) unchanged after 8h or 24h.

(v) 4-Cyano-2,5-diphenyloxazole 3-N-oxide boron trifluoride adduct (306e) was recovered (76-84%) unchanged after 8h or 24h.

4.5. Attempted Reduction of the Oxazole 3-N-Oxide Boron Trifluoride Adducts (302) and (306).

(a) Catalytic Hydrogenation.

A solution of 4,5-dimethyl-2-phenyloxazole 3-N-oxide boron trifluoride adduct (302a) (0.5 g) in acetonitrile (50.0 ml) was hydrogenated over 10% palladium on charcoal (0.1 g) for 1h. No uptake of hydrogen was observed and the adduct (302a) was recovered unchanged (80%) by filtering the reaction mixture and evaporating the filtrate.

(b) Sodium Dithionite.

The corresponding oxazole 3-N-oxide boron trifluoride adduct (302a), (306a-c) or (306e) (0.25 g) was heated under reflux in glacial acetic acid (5.0 ml) for 2h with twice its weight of sodium dithionite (added in two portions, the second portion after 1h). The reaction mixture was filtered hot to remove sodium dithionite. On cooling a small amount of sulphur precipitated and was removed by filtration. The filtrate was evaporated affording a residue which solidified on contact with ether. This salt-like material was washed with saturated aqueous sodium bicarbonate and filtered to afford the corresponding oxazole 3-N-oxide (301a), (305a) or (305c).

(i) 4,5-Dimethyl-2-phenyloxazole 3-N-oxide (301a), (80%), was identical (mixed m.p. and i.r. spectrum) with a sample prepared as described above.

(ii) 2,5-Diphenyl-4-methyloxazole 3-N-oxide (305a), (80%) was identical (mixed m.p. and i.r. spectrum) with a sample prepared as described above.

(iii) The solid obtained by treatment of 2,4-diphenyl-5-methyloxazole 3-N-oxide boron trifluoride adduct (306b) with sodium dithionite, as above, was washed with saturated aqueous sodium bicarbonate to give a dark oil which could not be solidified or characterised.

(iv) 2,5-Diphenyloxazole 3-N-oxide (305c), (68%), was identical (i.r. spectrum) with a sample obtained in 4.2., but decomposed on attempted crystallisation from benzene.

(v) The solid obtained by treatment of 4-cyano-2,5-diphenyloxazole 3-N-oxide boron trifluoride adduct (306e) with sodium dithionite as above, was washed with saturated aqueous sodium bicarbonate to give a brown solid (0.04 g), insufficient to characterise but whose i.r. spectrum indicated the presence of an amino-group.

4.6. Attempted Reaction of 4,5-Dimethyl-2-phenyloxazole 3-N-Oxide Boron Trifluoride Adduct (302a) with Phenyl Isocyanate.

The boron trifluoride adduct (302a) (0.005 mol) was suspended in chloroform (14.0 ml) and treated with phenyl isocyanate (0.005 mol) dropwise, with swirling. No apparent reaction had occurred after 1h at room temperature so fresh chloroform (6.0 ml) was added and the reaction mixture was heated under reflux for 30 min. Evaporation of the reaction mixture and trituration of the residue with ether afforded unchanged starting material (92%).

4.7. Reactions of Oxazole N-Oxides (30l) with Phenyl Isocyanate.

Solutions of the oxazole N-oxides (30la-h) (0.002 mol) in chloroform (5.0 ml) were treated dropwise with shaking and cooling in ice-water with phenyl isocyanate (0.002 mol). Vigorous gas evolution occurred. The reaction mixture was allowed to stand at room temperature for 1h and was then evaporated under reduced pressure to give a yellow gum. Trituration with ether yielded a white solid which was crystallised from benzene-light petroleum to give the corresponding 4-methylene-4,5-dihydroimidazole derivatives (316a-d), ^1H n.m.r. spectra, Table 8.

(i) 1,2-Diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) was obtained as white needles, (54%), m.p. 151° (from benzene-light petroleum), ν_{max} . 3050 (OH) and 1585 cm^{-1} .

Found: C, 77.7%; H, 6.3%; N, 10.6%; M, 264.

$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$ requires: C, 77.3%; H, 6.1%; N, 10.6%; M, 264.

(ii) 2-(p-Chlorophenyl)-5-hydroxy-5-methyl-4-methylene-1-phenyl-4,5-dihydroimidazole (316b) was obtained as white platelets, (68%), m.p. 160° (from benzene-light petroleum), ν_{max} . 3200 (OH) and 1600 cm^{-1} .

Found: C, 68.9%; H, 4.9%; N, 9.4%.

$\text{C}_{17}\text{H}_{15}\text{ClN}_2\text{O}$ requires: C, 68.3%; H, 5.0%; N, 9.4%.

(iii) 2-(p-Anisyl)-5-hydroxy-5-methyl-4-methylene-1-phenyl-4,5-dihydroimidazole (316c) was obtained as white platelets, (54%), m.p. 151° (from benzene-light petroleum), ν_{max} . 3150 (OH) and 1610 cm^{-1} .

Found: C, 73.6%; H, 6.1%; N, 9.9%.

C₁₈H₁₈N₂O₂ requires: C, 73.5%; H, 6.2%; N, 9.5%.

(iv) 5-Hydroxy-5-methyl-4-methylene-1-phenyl-2-(p-tolyl)-4,5-dihydroimidazole (316d) was obtained as white platelets, (50%), m.p. 152° (from benzene-light petroleum), ν_{max} . 3175 (OH) and 1615 cm⁻¹.

Found: C, 77.5%; H, 6.4%; N, 10.4%.

C₁₈H₁₈N₂O requires: C, 77.7%; H, 6.5%; N, 10.1%.

(v) Similar reaction of compound (301a) with p-chlorophenyl isocyanate afforded 1-(p-chlorophenyl)-5-hydroxy-5-methyl-4-methylene-2-phenyl-4,5-dihydroimidazole (325) as a white solid, (57%), m.p. 157° (from benzene), ν_{max} . 3050-3150 br (OH) and 1590 cm⁻¹.

Found: C, 68.9%; H, 5.0%; N, 9.1%.

C₁₇H₁₅ClN₂O requires: C, 68.3%; H, 5.0%; N, 9.4%.

(vi) Attempted reaction of 2-(o-hydroxyphenyl)-, 2-(m-nitrophenyl)-, and 2-(p-nitrophenyl)-4,5-dimethyloxazole 3-N-oxides (301e-g) with phenyl isocyanate, as above, resulted in recovery of the starting N-oxides (76%, 53% and 87% respectively). Heating the reaction mixtures under reflux for 4-5h resulted in the formation of an intractable gum from (301e), recovery of the N-oxide (301f) (53%), and from the N-oxide (301g), a gum containing four components (T.L.C. on silica in benzene-ether) which could not be separated by column chromatography on deactivated alumina, together with unchanged N-oxide (21%).

(vii) Attempted reaction of 2-(p-N,N-dimethylaminophenyl)-4,5-dimethyloxazole 3-N-oxide (301h) with phenyl isocyanate

afforded a red gum. Trituration with ether-ethanol afforded a trace amount of unchanged N-oxide, but the remaining gum could not be solidified. The ^1H n.m.r. spectrum of the gum provided no further information on the constitution of the gum.

4.8. Attempted Reaction of 4,5-Dimethyl-2-phenyloxazole 3-N-Oxide (301a) with Methyl Isocyanate.

(a) Attempted reaction of 4,5-dimethyl-2-phenyloxazole 3-N-oxide (301a) with methyl isocyanate, as described above for phenyl isocyanate, afforded the starting N-oxide (66%).

(b) Heating the reaction mixture under reflux for 4h gave a pale yellow solution. Evaporation afforded a yellow gum which would not solidify on treatment with organic solvents, and whose ^1H n.m.r. spectrum indicated the presence of several components. No attempt was made to separate the mixture.

4.9. Attempted Reaction of 4,5-Dimethyl-2-phenyloxazole 3-N-Oxide (301a) with Phenyl Isothiocyanate.

Attempted reaction of the N-oxide (301a) with phenyl isothiocyanate, as described above for phenyl isocyanate, gave a red solution. Evaporation of the reaction mixture afforded an oil, which would not solidify in contact with organic solvents. The presence of several components was indicated by the ^1H n.m.r. spectrum of the oil. No attempt was made to separate the mixture.

4.10. Catalytic Hydrogenation of 1,2-Diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a).

A solution of 1,2-diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) (0.001 mol) in ethanol was hydrogenated over 10% palladium-charcoal (0.05 g) at atmospheric pressure until 0.001 mol of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent was evaporated under reduced pressure affording a colourless oil. Trituration with ether yielded 4,5-dimethyl-1,2-diphenyl-5-hydroxy-4,5-dihydroimidazole (320), (63%), as white prisms, m.p. 110° (from benzene-light petroleum), ν_{\max} . 3175 br (OH) cm^{-1} , τ (CDCl_3) 2.65-3.18 (10H, m, Ar-H), 5.68 (1H, s, OH), 5.93 (1H, q, J 7.0 Hz, CH), 8.61 (3H, s, 5- CH_3) and 8.71 (3H, d, J 7.0 Hz, 4- CH_3). Irradiation at τ 5.93 caused the doublet at τ 8.71 to collapse to a singlet, and irradiation at τ 8.71 caused the quartet at τ 5.93 to collapse to a singlet (see Figure 38).

Found: N, 10.0%; M^+ , 266.

$\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}$ requires: N, 10.5%; M, 266.

When the product (320) was allowed to stand in contact with the solvent, dehydration occurred to afford 4,5-dimethyl-1,2-diphenylimidazole (321), (32%), m.p. 90° , M^+ 248.131812, $\text{C}_{17}\text{H}_{16}\text{N}_2$ requires 248.131342, τ (CDCl_3) 2.50-2.95 (10H, m, Ar-H), 7.73 (3H, s, CH_3) and 8.02 (3H, s, CH_3), identical (m.p., mixed m.p. i.r. and n.m.r. spectra) with an authentic sample¹⁸⁷ (lit.,¹⁸⁷ m.p. 90°).

4.11. Alkaline Hydrolysis of 1,2-Diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a).

(a). Using 10% Aqueous Sodium Hydroxide.

(i) A solution of 1,2-diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) (0.001 mol) in ethanol (2.0 ml) was treated with 10% aqueous sodium hydroxide (2.0 ml) and left at room temperature for 24h. Partial evaporation and filtration afforded the starting imidazole (68% recovery).

(ii) A solution of 1,2-diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) (0.002 mol) in ethanol (5.0 ml) was treated with 10% aqueous sodium hydroxide (4.0 ml) and heated under reflux for 0.5h giving a dark red solution. Partial evaporation and filtration afforded benzanilide (0.02 g, 8%) identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample. The filtrate was extracted with chloroform, to afford aniline (0.01 g, 6%), identical (i.r. spectrum) with an authentic sample. The aqueous extract was acidified with dilute sulphuric acid, affording a precipitate of benzoic acid, more of which (total, 0.19 g, 82%) was obtained by chloroform extraction of the acidic mother liquors.

(b) N Aqueous Sodium Carbonate.

A solution of 1,2-diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) (0.002 mol) in ethanol (4.0 ml) was treated with N sodium carbonate (4.0 ml) and the reaction mixture was heated under reflux. Partial evaporation and filtration afforded unchanged imidazole (316a) (quantitative recovery after 5 min heating; 64% recovery after 30 min heating).

4.12. Isomerisation of 4-Methylene-4,5-dihydroimidazoles (316a-d) and (325) to 4-hydroxymethylimidazoles (322a-d) and (326).

A solution of the 4-methylene-4,5-dihydroimidazole (316a-d) or (325) (0.5 g) in 2 N aqueous sulphuric acid (2.5 ml) was heated under reflux for 30 min. The reaction mixture was filtered to remove trace amounts of insoluble material (1-2%) and neutralised with 10% aqueous sodium hydroxide. The white precipitate was extracted into chloroform and the dried (MgSO_4) extracts evaporated to give the corresponding 4-hydroxymethylimidazole (322a-d) or (326), ν_{max} . 3200-3150 (OH) and 1615-1610 cm^{-1} . ^1H n.m.r. spectra, Table 9.

(i) 1,2-Diphenyl-4-hydroxymethyl-5-methylimidazole (322a) was obtained as a white solid, (87%), m.p. 207° (from benzene).

Found: C, 77.4%; H, 5.9%; N, 10.6%.

$\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$ requires: C, 77.3%; H, 6.1%; N, 10.6%.

(ii) 2-(p-Chlorophenyl)-4-hydroxymethyl-5-methyl-1-phenylimidazole (322b) was obtained as white prisms, (94%), m.p. 178° (from benzene-light petroleum).

Found: C, 68.0%; H, 4.7%; N, 9.3%.

$\text{C}_{17}\text{H}_{15}\text{ClNO}_2$ requires: C, 68.3%; H, 5.0%; N, 9.4%.

(iii) 2-(p-Anisyl)-4-hydroxymethyl-5-methyl-1-phenylimidazole (322c) was obtained as a white solid, (94%), m.p. 206° (from benzene-light petroleum).

Found: C, 73.0%; H, 6.1%; N, 9.4%.

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_2$ requires: C, 73.5%; H, 6.2%; N, 9.5%.

(iv) 4-Hydroxymethyl-5-methyl-1-phenyl-2-(p-tolyl)-imidazole (322d) was obtained as white platelets, (64%), m.p. 190°

(from benzene-light petroleum).

Found: C, 77.9%; H, 6.3%; N, 9.9%.

C₁₈H₁₈N₂O requires: C, 77.7%; H, 6.5%; N, 10.1%.

(v) 1-(p-Chlorophenyl)-4-hydroxymethyl-5-methyl-2-phenyl-imidazole (326) was obtained as white needles in quantitative yield, m.p. 218° (from ethanol-water).

Found: C, 68.6%; H, 5.0%; N, 8.9%.

C₁₇H₁₅ClN₂O requires: C, 68.3%; H, 5.0%; N, 9.4%.

4.13. Other Allylic Rearrangements of 1,2-Diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a).

A solution of 1,2-diphenyl-5-hydroxy-5-methyl-4-methylene-4,5-dihydroimidazole (316a) (0.001 mol) in (i) glacial acetic acid (3.0 ml), (ii) methanol (3.0 ml), or (iii) ethanol (3.0 ml) was treated with concentrated sulphuric acid (0.3 ml). The reaction mixture was heated under reflux for 30 min, partially evaporated under reduced pressure and diluted with water. Neutralisation with 10% aqueous sodium hydroxide or, in (i), with dilute ammonium hydroxide, afforded a semi-solid which solidified on standing with occasional rubbing.

(i) 4-Acetoxymethyl-1,2-diphenyl-5-methylimidazole (327a) was obtained as white needles, (58%), m.p. 121° (from light petroleum), ν_{\max} . 1720 (CO) cm^{-1} , τ (CDCl₃) 2.56-2.86 (10H, m, Ar-H), 4.83 (2H, s, CH₂), 7.90 (3H, s, CH₃) and 7.95 (3H, s, OAc).

Found: C, 73.5%; H, 6.0%; N, 9.2%.

C₁₉H₁₈N₂O₂ requires: C, 74.5%; H, 5.9%; N, 9.2%.

The compound (327a) was identical (m.p., mixed m.p. and i.r. spectrum) with a sample obtained, (80%), by warming 1,2-diphenyl-4-hydroxymethyl-5-methylimidazole (322a) with acetic anhydride.

(ii) 1,2-Diphenyl-4-methoxymethyl-5-methylimidazole (327b) was obtained as cream prisms, (quantitative yield), m.p. 124° (from benzene-light petroleum), ν_{\max} . 1600 cm^{-1} , τ (CDCl_3) 2.56-2.88(10H, m, Ar-H), 5.51 (2H, s, CH_2), 6.52 (3H, s, OCH_3) and 7.90 (3H, s, CH_3).

Found: C, 76.4%; H, 6.2%; N, 10.4%.

$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}$ requires: C, 77.7%; H, 6.5%; N, 10.1%.

1,2-Diphenyl-4-hydroxymethyl-5-methylimidazole (322a) treated with methanolic sulphuric acid, as above, was recovered unchanged (95%).

(iii) Heating under reflux with 95% or anhydrous ethanol afforded 1,2-diphenyl-4-hydroxymethyl-5-methylimidazole (322a), (10%), identical (m.p., mixed m.p. and i.r. spectrum) with an authentic sample. The remaining gummy material could not be solidified or characterised.

4.14. Preparation of 4,5-Dimethyl-1,2-diphenylimidazole (321).

(a) N-phenylbenzamidine,²⁰⁸ (47%), had m.p. 113° (lit.,²⁰⁸ 115°).

The attempted preparation of 4,5-dimethyl-1,2-diphenylimidazole (321) by heating acetoin (0.01 mol) and N-phenylbenzamidine (0.01 mol) in ethanol (20.0 ml) under reflux on a water bath for 5h, resulted in recovery (65%) of N-phenylbenzamidine.

(b) The preparation of compound (321) according to the method of Goto et al.¹⁸⁷ afforded a gum which was purified by column chromatography, with the difference that the alumina column was eluted with toluene-ether (1:1) affording 4,5-dimethyl-1,2-diphenylimidazole (321), (40%), m.p. 90° (from light petroleum) (lit.,¹⁸⁷ 90°), identical (m.p., mixed m.p., i.r. and n.m.r. spectra) with a sample obtained as described above.

4.15. Attempted Condensation of N-Phenylbenzamidine with Biacetyl.

N-Phenylbenzamidine (0.002 mol) suspended in water (5.0 ml), or dissolved in ethanol (5.0 ml) was treated with biacetyl (0.002 mol). 50% aqueous potassium hydroxide was added dropwise until the reaction mixtures were alkaline. After 15 min at room temperature the resulting dark brown reaction mixtures were worked up to afford unchanged N-phenylbenzamidine (96% and 57% respectively). Acidification and extraction of the mother liquors with chloroform afforded no further material.

Table 7
Assignments^{a,b} (τ) of ^1H n.m.r. Resonance Signals of Oxazole 3-N-Oxides
and their Hydrochlorides and Boron Trifluoride Adducts.

Compd.	CH_3	Ar-H	Others	Compd.	CH_3	Ar-H	Others
(300a)	7.52s) 7.59s)	1.75dd) 2.32 - 2.56m)	-	(302g)	7.57s) 7.74s)	1.43d) 1.71d)	-
(300b)	7.52s) 7.57s)	1.73d) 2.45d)	-	(302h)	7.71s) 7.83s)	1.68d) 3.25d)	6.99s ^d
(300e)	7.54s	1.80d) 2.62d)	-	(305a)	7.49s	1.42 - 1.52m) 2.28 - 2.64m)	-
(300h)	7.68s) 7.74s)	1.83d) 3.29d)	4.75s ^c 6.96s ^d	(305f)	7.45s) 8.84t ^f)	2.12 - 2.58m	5.77q ^{f,g}
(300j)	7.14s) 7.57s) 7.68s)	-	-	(308)	7.31s	2.30-2.76m	-
(304a)	7.30s	1.62dd) 2.30 - 2.52m)	-	(302a)	7.57s) 7.66s)	1.72dd) 2.37 - 2.49m)	-
(304d)	7.45s	1.73dd) 2.28 - 2.50m)	2.00s ^e	(302j)	7.26s) 7.63s) 7.75s)	-	-
(304f)	7.20s) 8.58t ^f)	1.64dd) 2.28 - 2.40m)	5.56q ^{f,g}	(306a)	7.38s	1.57dd) 2.26 - 2.54m)	-
(307)	6.98s	2.25 - 2.62m	-	(306b)	7.50s	1.50 - 1.75m) 2.32 - 2.58m)	-
(301a)	7.73s) 7.85s)	1.55 - 1.65m) 2.47 - 2.67m)	-	(306c) ^j	-	1.58dd) 2.08 - 2.40m)	1.92s ^e
(302b)	7.68s) 7.83s)	1.64d) 2.60d)	-	(306d)	7.50s	1.70dd) ^k 2.40m)	-
(302c)	7.71s) 7.88s)	2.48 - 2.76m) 3.04 - 3.28m)	-	(306f)	7.26s) 8.56t ^f)	1.58dd) 2.28 - 2.42m)	5.53q ^{f,g}
(302d)	7.70s) 7.82s)	1.61d) 3.03d)	6.18s ^h	(306h)	8.56t ^f	1.40 - 1.65m) 1.90 - 2.45m)	5.47q ^{f,g}
(302e)	7.63s) 7.71s) 7.83s)	1.67d) 2.75d)	-	(309)	7.08s	2.40 - 2.68m	-
(302f)	7.58s) 7.78s)	0.86t 1.17dd 1.77dt 2.35t	-				

^a Spectra taken at 100 MHz in deuterochloroform at 28° with tetramethylsilane as internal standard. Chemical shifts are given in p.p.m. downfield from tetramethylsilane to the centre of multiplets and are measured to an accuracy of ± 0.01 p.p.m.; s = singlet; d = doublet; dd = double doublet; t = triplet; dt = double triplet; q = quartet; m = multiplet.

^b J_{ortho} and J_{meta} were in the ranges 8.0 - 9.0 and 1.0 - 1.5 Hz respectively.

^c OH; ^d N-CH₃;
^e H-4; ^f $J = 7.0$ Hz; ^g CH₂; ^h OCH₃;

^j Spectrum taken in trifluoroacetic acid
^k Ar (H) - H(4).

Table 8

Assignments^a (τ) of ^1H n.m.r. Resonance Signals of 4-Methylene-4,5-dihydroimidazoles (316a-d) and (325).

Compd.	= CH ₂	5-CH ₃	OH	Ar-H	Others
(316a)	4.89s) 5.40s)	8.79s	-	2.55 - 3.20m	-
(316b)	4.89s) 5.38s)	8.79s	4.20br	2.60 - 3.20m	-
(316c)	4.93s) 5.42s)	8.78s	-	2.60 - 3.35m	6.23s ^b
(316d)	4.90s) 5.40s)	8.79s	4.55br	2.65 - 3.20m	7.70s ^c
(325)	4.88s) 5.37s)	8.80s	4.00br	2.60 - 3.45m	-

a - c See below Table 9.

Table 9

Assignments^a (τ) of ^1H n.m.r. Resonance Signals of 4-Hydroxymethyl-imidazoles (322a-d) and (326)

Compd.	CH ₂	5-CH ₃	OH	Ar-H	Others
(322a)	5.31s	7.93s	6.10br	2.55 - 2.92m	-
(322b)	5.32s	7.94s	-	2.50 - 2.95m	-
(322c)	5.32s	7.94s	-	2.54 - 3.36m	6.30s ^b
(322d)	5.31s	7.94s	5.85br	2.63 - 3.14m	7.77s ^c
(326)	5.32s	7.93s	-	2.50 - 2.94m	-

^a Spectra taken at 100 MHz in deuterochloroform at 28° with tetramethylsilane as internal standard.

Chemical shifts are given in p.p.m. downfield from tetramethylsilane.

^b OCH₃;

^c CH₃.

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APPENDIX

Heterocyclic *N*-Oxides. Part VI.¹ Synthesis and Nuclear Magnetic Resonance Spectra of 3-Aminobenzo-1,2,4-triazines and their Mono- and Di-*N*-oxides

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Heterocyclic *N*-Oxides. Part VI.¹ Synthesis and Nuclear Magnetic Resonance Spectra of 3-Aminobenzo-1,2,4-triazines and their Mono- and Di-*N*-oxides

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A series of 3-aminobenzo-1,2,4-triazine derivatives has been synthesised and their oxidation with hydrogen peroxide in acetic acid studied. The position of the *N*-oxide group(s) in the products has been established by analysis of n.m.r. spectra. It is shown that oxidation of 3-aminobenzo-1,2,4-triazines at room temperature leads almost exclusively to the 2-oxide whereas prolonged oxidation at 50° yields the 1,4-di-*N*-oxide.

Few investigations of the peracid oxidation of the benzo-1,2,4-triazine ring system have been reported. The available information suggests that depending on the conditions both mono- and di-*N*-oxides are formed. Oxidation of 3-aminobenzo-1,2,4-triazine and some of its derivatives at 50° with hydrogen peroxide in acetic acid is reported² to afford red dioxides tentatively assigned² 1,4-di-*N*-oxide structures (V). Oxidation at room temperature² on the other hand led to mono-*N*-oxides isomeric with the 1-oxides of established³⁻⁵ structure.

continuing interest⁷ in the chemistry of benzotriazines prompted a re-examination of the peracid oxidation of 3-aminobenzo-1,2,4-triazine derivatives. The initial results are now described. The structures of the products of peracid oxidation have been firmly established by n.m.r. spectroscopy. In general it is now shown that oxidation of 3-aminobenzo-1,2,4-triazines at room temperature leads almost exclusively to the 2-oxide whereas prolonged oxidation at 50° yields the 1,4-di-*N*-oxide.

The condensation^{3,4} of *o*-nitroaniline derivatives with

TABLE I
3-Aminobenzo-1,2,4-triazines

Compd.	Yield (%)	M.p. ^a	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(IIa)	63	207 (207°)	—	—	—	—	—	—	—
(IIb)	87	218 (218)	59.8	4.9	35.4	C ₈ H ₈ N ₄	60.0	5.0	35.0
(IIc)	84	222 (222)	54.4	4.5	32.0	C ₈ H ₈ N ₄ O	54.5	4.5	31.8
(IId)	73	255 (255)	—	—	—	—	—	—	—
(IIe)	80	286	61.5	5.7	31.7	C ₉ H ₁₀ N ₄	62.1	5.7	32.2

^a M.p.s in parentheses denote literature^{3,6} values.

On the basis of their further transformation by hydrogen peroxide into the corresponding 1,4-di-*N*-oxides, these mono-oxides were assigned² the 4-oxide structure (IV). However the orientation of the red dioxides was not established, making the structure of the mono-oxides likewise uncertain. Moreover the product obtained by peracid oxidation of 3-aminobenzo-1,2,4-triazine at room temperature has been formulated as the 2-oxide.⁶ These conflicting reports on the nature of the products and our

cyanamide provided a convenient route to 3-aminobenzo-1,2,4-triazine 1-*N*-oxides (I) (Table 2), in which the position of the *N*-oxide group is known with certainty. Dithionite reduction of the 1-*N*-oxides (I) afforded the parent 3-aminobenzo-1,2,4-triazines (II) (Table 1) in high yield.

The site of *N*-oxidation or quaternisation of azaheterocycles can be established by studying changes in chemical shift produced in the magnetic resonance of protons in

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TABLE 2
3-Aminobenzo-1,2,4-triazine mono-*N*-oxides

Compd.	Yield (%)	M.p. ^a	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(Ia)	80	275 (271°)	—	—	—	—	—	—	—
(Ib)	66	271 (271)	54.3	4.6	31.8	C ₈ H ₈ N ₄ O	54.5	4.5	31.8
(Ic)	81	271 (281)	—	—	—	—	—	—	—
(Id)	39	312 (303)	—	—	—	—	—	—	—
(Ie)	75	288 (decomp.)	56.3	5.3	29.1	C ₉ H ₁₀ N ₄ O	56.8	5.3	29.5
(IIa)	46	200 (187)	51.3	3.6	34.6	C ₇ H ₈ N ₄ O	51.8	3.7	34.6
(IIb)	76	203	54.6	4.5	31.5	C ₈ H ₈ N ₄ O	54.5	4.5	31.8
(IIc)	39	196 (183)	50.2	4.4	29.1	C ₈ H ₈ N ₄ O ₂	50.0	4.2	29.2
(IId)	35	223 (215)	42.7	2.6	28.5	C ₇ H ₈ ClN ₄ O	42.6	2.5	28.4
(IIe)	84	238	57.3	5.4	29.6	C ₉ H ₁₀ N ₄ O	56.8	5.3	29.5

^a M.p.s in parentheses denote literature ²⁻⁶ values.

TABLE 3
3-Aminobenzo-1,2,4-triazine 1,4-di-*N*-oxides

Compd.	Yield (%)	M.p. ^a	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(Va)	89	220 (230°)	46.7	3.3	31.8	C ₇ H ₈ N ₄ O ₂	47.2	3.4	31.5
(Vb)	71	220	50.2	4.2	29.3	C ₈ H ₈ N ₄ O ₂	50.0	4.2	29.2
(Vc)	71	225 (214)	45.3	3.9	26.7	C ₈ H ₈ N ₄ O ₃	46.2	3.8	26.9
(Vd)	62	269 (295)	39.3	2.6	26.1	C ₇ H ₈ ClN ₄ O ₂	39.4	2.5	26.3
(Ve)	74	242	51.7	5.0	26.7	C ₉ H ₁₀ N ₄ O ₂	52.4	4.9	27.2
(VIa)	—	190	49.2	3.6	25.6	C ₉ H ₈ N ₄ O ₃	49.1	3.6	25.5
(VIb)	—	212	51.3	4.4	23.9	C ₁₀ H ₁₀ N ₄ O ₃	51.3	4.3	23.9
(VIc)	—	219	48.6	4.0	22.0	C ₁₀ H ₁₀ N ₄ O ₄	48.0	4.0	22.4
(VId)	—	213	42.5	2.8	22.1	C ₈ H ₈ ClN ₄ O ₃	42.3	2.8	22.0
(VIE)	—	197	52.9	4.8	22.5	C ₁₁ H ₁₂ N ₄ O ₃	53.2	4.8	22.6

^a M.p.s in parentheses denote literature ² values.

TABLE 4
Assignments ^{a,b} (τ) of ¹H n.m.r. resonance signals of 3-aminobenzo-1,2,4-triazines and their mono- and di-*N*-oxides

Compd.	H(5)	H(6)	H(7)	H(8)	OMe	CMe	COMe	NH ₂
(Ia)	2.21m ^e	1.86td	2.21m ^e	1.55dd	—	—	—	—
(Ib)	2.33d	2.01dd	—	1.78s	—	7.39s	—	—
(Ic)	2.24m ^d	2.24m ^d	—	2.24m ^d	5.97s	—	—	—
(Id)	2.20d	1.94dd	—	1.65d	—	—	—	—
(Ie)	2.45s	—	—	1.82s	—	{ 7.40s 7.46s	—	—
(IIa)	2.13m ^e	1.74m ^e	2.13m ^e	1.74m ^e	—	—	—	—
(IIb)	2.26d	1.87dd	—	2.03s	—	7.35s	—	—
(IIc)	2.28d	2.04dd	—	2.77d	5.91s	—	—	—
(IId)	2.22dd	(1.90)	—	(1.79)	—	—	—	—
(IIe)	2.39s	—	—	2.09	—	{ 7.31s 7.43s	—	—
(IIIa)	2.21m ^e	1.99m ^e	2.21m ^e	1.99m ^e	—	—	—	—
(IIIb)	2.30d	2.13dd	—	2.19dd	—	7.39s	—	—
(IIIc)	2.25m ^f	2.25m ^f	—	2.68s	5.96s	—	—	—
(IIId)	2.30d	2.12m ^e	—	2.12m ^e	—	—	—	—
(IIIe)	2.36s	—	—	2.20s	—	{ 7.38s 7.45s	—	—
(Va)	1.91dd	1.71td	2.16td ^f	1.56dd	—	—	—	2.16 ^f
(Vb)	1.96s ^f	1.96s ^f	—	1.75s	—	7.36	—	2.34
(Vc)	1.92d	2.13dd	—	2.25d	5.95s	—	—	2.46
(Vd)	1.89s ^f	1.89s ^f	—	1.61s	—	—	—	2.21
(Ve)	2.11s	—	—	1.81s	—	{ 7.35s 7.45s	—	—
(VIa)	← 1.38—2.26m ^h →				—	—	7.34s	—
(VIb)	← 1.47—1.91m ^h →				—	← { 7.29s 7.33s } →	—	—
(VIc)	1.59d	2.08dd	—	2.20d	5.90s	—	7.36s	—
(VId)	1.54m ⁱ	1.88dd	—	1.54m ⁱ	—	—	7.37s	—
(VIE)	1.76s	—	—	1.71s	—	← { 7.31s 7.33s 7.37s } →	—	—

^a Spectra taken at 100 MHz on a Varian HA 100 instrument in trifluoroacetic acid at 28° with tetramethylsilane as internal standard. Chemical shifts are given in p.p.m. downfield from tetramethylsilane to centre of multiplets and are measured to an accuracy of ±0.01 p.p.m.; s = singlet; d = doublet; dd = double doublet; td = triple doublet; m = multiplet. ^b *J*_{5,6} and *J*_{6,8} were in the ranges 7.5–9.4 and 1.3–2.5 Hz respectively. ^c H(5)–H(7). ^d H(5)–H(6)–H(8). ^e H(6)–H(8). ^f H(5)–H(6). ^g H(7)–NH₂. ^h H(5)–H(6)–H(7)–H(8). ⁱ H(5)–H(8).

Figures in parentheses denote approximate values.

the vicinity of the reaction site. The downfield shift of H(8) in cinnoline 1-oxide compared with cinnoline is due to the deshielding effect of the adjacent *N*-oxide group.^{8,9} This effect is clearly demonstrated by the chemical shift data (Table 4) obtained from the ¹H n.m.r. spectra of 3-aminobenzo-1,2,4-triazines (II) and their 1-*N*-oxides (I). The simplest situation is found in the dimethyl derivatives (Ie) and (IIf) whose spectra (Figure 1) are uncomplicated by spin-spin splitting (no attempt was made to detect Me-H splitting). The signal at lowest

TABLE 5

Effects of *N*-oxidation on proton chemical shiftsProton shifts* (p.p.m.) of 3-aminobenzo-1,2,4-triazine *N*-oxides compared with the corresponding 3-aminobenzo-1,2,4-triazines (II)

Compd.	H(5)	H(6)	H(7)	H(8)
(Ia)	(+0.08)	(+0.12)	(+0.08)	(-0.17)
(Ib)	+0.07	+0.14	—	-0.25
(Ic)	(-0.04)	(+0.20)	—	(-0.53)
(Id)	-0.02	(+0.04)	—	(-0.14)
(Ie)	+0.06	—	—	-0.27
(IIIa)	(+0.08)	(+0.25)	(+0.08)	(+0.25)
(IIIb)	+0.04	+0.26	—	+0.16
(IIIc)	(-0.03)	(+0.21)	—	-0.09
(IIId)	+0.08	(+0.22)	—	(+0.33)
(IIIe)	-0.03	—	—	+0.11
(Va)	(-0.22)	(-0.03)	(+0.03)	(-0.18)
(Vb)	-0.30	+0.09	—	-0.28
(Vc)	-0.36	+0.08	—	-0.52
(Vd)	-0.33	(-0.01)	—	(-0.18)
(Ve)	-0.28	—	—	-0.29
(VIa)	—	—	—	—
(VIb)	(-0.31) ^b	(+0.04) ^b	—	(-0.11)
(VIc)	-0.69	+0.04	—	-0.57
(VId)	(-0.68)	(-0.10)	—	(-0.25)
(VIe)	-0.63	—	—	-0.38

* Values in parenthesis are approximate. ^b Minimum approximate values.

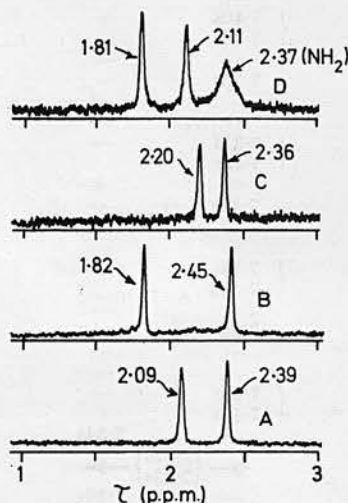


FIGURE 1 ¹H N.m.r. spectra of compound (IIe) A, (Ie) B, (IIIe) C, and (Ve) D, (trifluoroacetic acid; 100 MHz)

field in both cases may be attributed to H(8) which in benzo-1,2,4-triazines is more deshielded than H(5).¹⁰ This assignment is supported by the downfield shift (ca.

⁸ M. Ogata, H. Kano, and K. Tori, *Chem. and Pharm. Bull. (Japan)*, 1963, **11**, 1527.

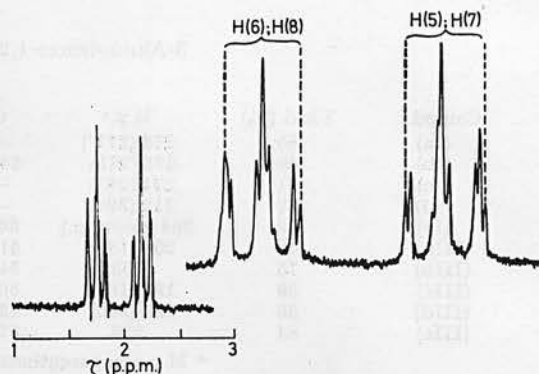


FIGURE 2 ¹H N.m.r. spectrum of compound (IIa) in trifluoroacetic acid at 100 MHz; inset expansion to 250 Hz

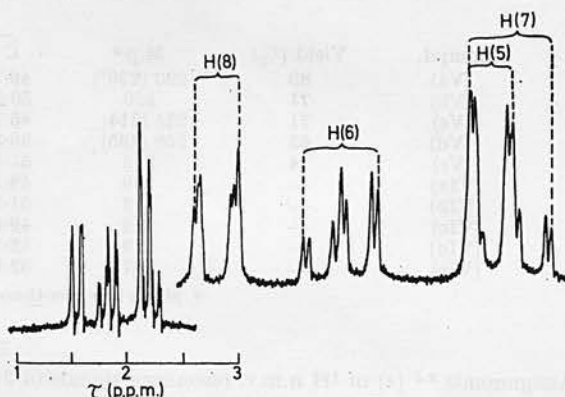


FIGURE 3 ¹H N.m.r. spectrum of compound (Ia) in trifluoroacetic acid at 100 MHz; inset expansion to 250 Hz

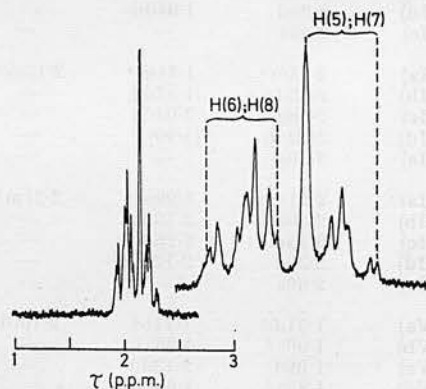


FIGURE 4 ¹H N.m.r. spectrum of compound (IIIa) in trifluoroacetic acid at 100 MHz; inset expansion to 250 Hz

0.2 p.p.m.) of H(8) in the 1-oxide (Ie) relative to H(8) in the benzotriazine (IIe) (Tables 4 and 5). In contrast, conversion of the parent compound (IIe) into the 1-oxide (Ie) has little effect on the chemical shift of H(5) (Tables 4 and 5). The same effects are found in the n.m.r. spectra of the monosubstituted benzotriazines (IIb-d) and

⁹ I. Suzuki, M. Nakadate, T. Nakashima, and N. Nagasawa, *Chem. and Pharm. Bull. (Japan)*, 1967, **15**, 1088.

¹⁰ K. Brenneisen, O. Thumm, and J. Benz, *Helv. Chim. Acta*, 1966, **49**, 651.

(Ib—d). The spectra of these compounds are complicated by spin-spin splitting in an ABX system. The first-order splitting pattern in the spectra of the compounds (Ib), (Id), and (IIb—c) permitted the assignment of the proton resonances shown (Table 4). These assignments are supported by the magnitude of the coupling constants (footnote to Table 4) obtained by first-order analysis. The chemical shift of H(5) and consequently $J_{5,6}$ and $J_{6,8}$ in the chloro-compound (IIId) were readily assigned from the splitting pattern in the n.m.r. spectrum (Table 4). The signals due to H(6) and H(8) on the other hand are merged, precluding the determination of

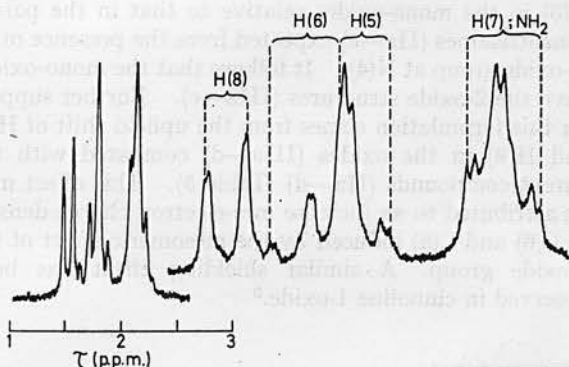


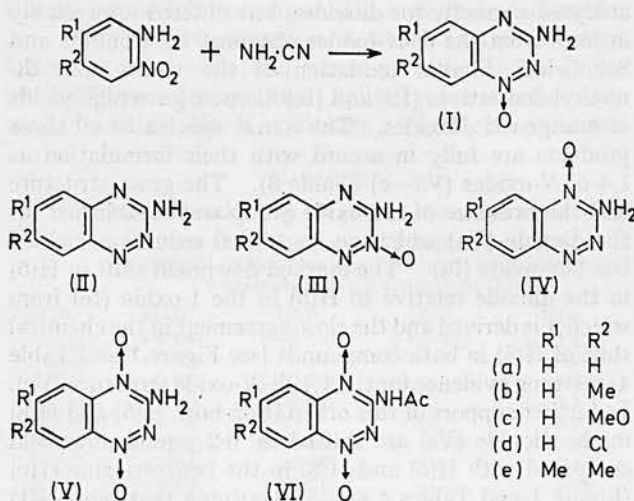
FIGURE 5 ^1H N.m.r. spectrum of compound (Va) in trifluoroacetic acid at 100 MHz; inset expansion to 250 Hz

accurate chemical shifts for these protons. Individual chemical shifts and coupling constants for H(5), H(6), and H(8) in the oxide (Ic) were likewise unobtainable owing to signal overlap. The n.m.r. spectrum of the oxide (Ia) (Figure 3) contains three groups of lines centred at τ 1.55, 1.86, and 2.21 in the integrated ratio 1 : 1 : 2 respectively. H(8) should appear at lowest field owing to the deshielding effect of the 1-oxide group. The mesomeric effect of the 3-amino-group should increase the π -electron density at C(5) and C(7) resulting in greater shielding of H(5) and H(7) relative to H(6). This reasoning in conjunction with the splitting pattern (Figure 3) allows the assignment of the signals in the spectrum of the oxide (Ia) to individual protons as shown (Table 4 and Figure 3). These assignments are supported by the magnitude of the corresponding coupling constants (footnote to Table 4) obtained from first-order splitting. The n.m.r. spectrum of the benzotriazine (IIa) (Figure 2) consists of two multiplets centred at τ 1.74 and 2.13 attributable to H(8)—H(6) and H(7)—H(5) respectively (Figure 2 and Table 4). The complexity of the spectrum prevented the determination of individual chemical shifts and coupling constants. Despite the greater complexity of the spectra the data in Table 4 clearly show that the chemical shift of H(5) in the parent compounds (IIa—d) and the corresponding 1-oxides (Ia—d) agree to within $\pm(0.02\text{--}0.08)$ p.p.m. (Table 5) whereas H(8) in the oxides experiences a downfield shift of 0.14—0.53 p.p.m. relative to H(8) in the parent benzotriazines (Table 5).

These results establish the deshielding effect of a 1-*N*-oxide group on H(8) of the benzo-1,2,4-triazine ring.

Prolonged oxidation of the 1-oxides (Ia) and (Ic—d) at 50° with hydrogen peroxide in acetic acid gave moderately high yields of orange-red products which analysed correctly for dioxides, but differed appreciably in m.p. from the di-*N*-oxides obtained by Robbins and Schofield.² Similar oxidation of the mono- and dimethyl derivatives (Ib) and (Ie) likewise gave high yields of orange-red dioxides. The n.m.r. spectra of all these products are fully in accord with their formulation as 1,4-di-*N*-oxides (Va—e) (Table 3). The gross structure and the presence of a 1-oxide group was established for the dioxide (Va) which on controlled reduction yielded the 1-*N*-oxide (Ia). The marked downfield shift in H(5) in the dioxide relative to H(5) in the 1-oxide (Ie) from which it is derived and the close agreement in the chemical shift of H(8) in both compounds (see Figure 1 and Table 4) is strong evidence for the 1,4-di-*N*-oxide structure (Ve). In further support of this orientation both H(5) and H(8) in the dioxide (Ve) are shifted *ca.* 0.2 p.p.m. downfield compared with H(5) and H(8) in the benzotriazine (IIe) (Figure 1 and Tables 4 and 5), verifying that both N(1) and N(4) are oxidised. The signal at τ 2.37 (Figure 1) in the 1,4-di-*N*-oxide (Ve) which is absent in the spectrum of the *N*-acetyl derivative (VIf) (Table 4) is attributable to the amino-group protons. The enhanced downfield shift in H(5) in the acetyl-amino-compound (VIf) compared with the amine (Ve) (Tables 4 and 5) is a measure of the greater deshielding effect of the 4-oxide group resulting from reduction in the basicity of the amino-centre. The n.m.r. spectra of the monosubstituted dioxides (Vb—d) are more complex. Analysis of first-order splitting was possible only for the spectrum of the methoxy-derivative (Vc) giving the chemical shifts and coupling constants shown (Tables 4 and 5). The appearance of H(5) at a lower field than H(8) in the spectrum of the methoxy-compound (Vc) is not unexpected in view of the powerful shielding effect at H(8) induced by the mesomeric effect of the methoxy-group. The lack of resolution in the n.m.r. spectra of the dioxides (Vb) and (Vd) precluded the determination of accurate chemical shifts and coupling constants, though in both cases the signal at low field may be attributed to H(8) (Table 4). With the exception of the methoxy-derivative (VIf), the spectra of the acetyl-amino-compounds (VIb—d) show little better resolution (Table 4). H(6) is assigned to the high-field signal in the spectrum of the chloro-compound, but otherwise chemical shifts and coupling constants were unobtainable for the aromatic protons in the compounds (VIb) and (VId). The signal due to the amino-group in the dioxides (Vb—d) is absent from the acetyl derivatives (VIb—d) (Table 4). Despite the lack of precision in the chemical shift data, the general pattern (Table 4) again shows that relative to H(5) and H(8) in the benzotriazines (IIb—d), H(5) and H(8) in the dioxides (Vb—d) show a marked downfield shift which is again enhanced for H(5) in the acetyl derivatives (VIb—d) (Table 5). The marked downfield shift of H(8)

in the dioxides compared with the 1-oxides (Ib—d) together with the close agreement in the chemical shift of H(8) in both types of oxide is further evidence for the 1,4-orientation (Vb—d) in the dioxides.



The n.m.r. spectrum of the dioxide derived from the 1-oxide (Ia) is shown in Figure 5. The assignments of the proton resonances obtained by analysis of first-order splittings shown in Table 4 are supported by the magnitude of the coupling constants (footnote to Table 4). Comparison with the data for the 1-oxide (Ia) (Table 4) demonstrates the correctness of the 1,4-di-*N*-oxide formulation (Va) for this dioxide. Thus, in accord with the presence of a 1-oxide group the chemical shift of H(8) is similar to that in the 1-*N*-oxide (Ia) (Tables 4 and 5). H(5) on the other hand shows the downfield shift compared with H(5) in the 1-*N*-oxide (Ia) expected from the presence of a 4-oxide group.

Peracid oxidation of the benzotriazines (IIa) and (IIc—d) at room temperature gave moderate yields of mono-*N*-oxides which differed somewhat in m.p. from the products reported by Arndt and Rosenau⁶ and Robbins and Schofield.² Similar peracid oxidation of the methyl derivatives (IIb) and (Iie) yielded mono-*N*-oxides isomeric with the 1-*N*-oxides (Ib) and (Ie) obtained previously. All these products were obtained pure in the yields shown (Table 2) after one crystallisation. In some cases the n.m.r. spectrum of the crude product revealed traces of the corresponding 1-oxide. Analysis of the n.m.r. spectra of these mono-*N*-oxides supports their formulation as 2-oxides (IIIa—e) rather than 2 4-oxides (IVa—e). In the n.m.r. spectrum of the oxide derived from the dimethyl compound (Iie) the low-field singlet is assigned to H(8) (see above) (Figure 1). Complete analysis of the first-order splitting in the n.m.r. spectra of the oxides derived from the monosubstituted compounds (IIb—d) was possible only in the case of the methyl derivative, giving the chemical shifts and coupling constants shown (Table 4). Signal overlap in the spectra of the oxides obtained from the methoxy- and chloro-

compounds (IIc) and (IId) prevented the assignment of accurate chemical shifts and coupling constants though consideration of the splitting patterns allowed the assignment of H(8) in the former compound and H(5) in the latter (Table 4). The complexity of the n.m.r. spectrum of the oxide derived from the benzotriazine (IIa) likewise precluded the determination of individual chemical shifts and coupling constants. However comparison with the spectra of the compounds (Ia), (IIa), and (Va) (Figures 2, 3, and 5) allows the low-field multiplet to be assigned to H(6)—H(8) and that at higher field to H(5)—H(7) (Figure 4). Consideration of the n.m.r. data (Table 4) clearly shows the lack of a marked downfield shift of H(5) in the mono-oxides relative to that in the parent benzotriazines (IIa—e) expected from the presence of an *N*-oxide group at N(4). It follows that the mono-oxides have the 2-oxide structures (IIIa—e). Further support for this formulation comes from the upfield shift of H(6) and H(8) in the oxides (IIIa—d) compared with the parent compounds (IIa—d) (Table 5). This effect may be attributed to an increase in π -electron charge density at C(6) and C(8) induced by the mesomeric effect of the 2-oxide group. A similar shielding effect has been observed in cinnoline 1-oxide.⁹

EXPERIMENTAL

I.r. spectra were recorded for Nujol suspensions with a Unicam SP 200 spectrophotometer.

3-Aminobenzo-1,2,4-triazine 1-*N*-Oxides (I).—A mixture of the *o*-nitroaniline derivative (0.072 mole) and cyanamide (20.0 g., 0.144 mole) was warmed at 100° giving a melt which was cooled to room temperature, treated with concentrated hydrochloric acid (25.0 ml.), and warmed briefly at 100° until a vigorous reaction occurred. After cooling to room temperature the mixture was treated with a solution of sodium hydroxide (20.0 g.) in water (25.0 ml.) and warmed at 100° for 0.5 hr. The yellow solid which separated on cooling and dilution with water was collected and crystallised from acetic acid to yield the 1-*N*-oxides (I) (Table 2), ν_{\max} . 3350 and 3150 (NH), 1655—1645, and 1555—1545 cm.⁻¹.

3-Aminobenzo-1,2,4-triazines (II).—The 1-*N*-oxide (II) (0.005 mole) was heated under reflux with twice its weight of sodium dithionite in 70% (v/v) aqueous ethanol (80.0 ml.) for 1.0 hr. Hot filtration and concentration of the reaction mixture yielded a solid which was washed with water, dried, and crystallised from ethanol or acetic acid to give the benzotriazine derivatives (II) (Table 1), ν_{\max} . 3300 and 3150 (NH), 1675—1660, and 1560—1545 cm.⁻¹.

3-Aminobenzo-1,2,4-triazine 1,4-Di-*N*-oxides (V).—A suspension of the 1-*N*-oxide (I) (0.005 mole) in acetic acid (25—100 ml.) was stirred and heated at 45—50° for 20—60 hr. with 30% aqueous hydrogen peroxide (12.5—25.0 ml.). The suspended solid slowly dissolved giving a clear red solution. The mixture was treated with solid sodium hydrogen carbonate to yield a red solid which was combined with material recovered by extracting the aqueous mother-liquors with chloroform, and crystallised from acetic acid-water to give the pure di-*N*-oxide (V) (Table 3), ν_{\max} . 3400, 3250, and 3200 (NH), and 1630—1600 cm.⁻¹.

The di-*N*-oxide (Va) heated under reflux with sodium dithionite in 70% (v/v) aqueous ethanol for 20 min. afforded

3-aminobenzo-1,2,4-triazine 1-*N*-oxide (Ia) (50%), m.p. 275° (from acetic acid) (lit.,² 271°), identical (mixed m.p. and i.r. spectrum) with an authentic sample.

The di-*N*-oxides (V) warmed with acetic anhydride afforded the corresponding *monoacetyl derivatives* (VI) (67—84%) (Table 3), which crystallised from ethanol or acetic acid–water, ν_{\max} 3300—3250 (NH), 1720 (CO), and 1550—1540 cm^{-1} .

3-Aminobenzo-1,2,4-triazine 2-*N*-Oxides (III).—(a) A suspension of the 3-aminobenzo-1,2,4-triazine (IIa), (IIb), or (IIe) (0.003 mole) in glacial acetic acid (10—20 ml.) was stirred at room temperature for 46 hr. with 30% aqueous hydrogen peroxide (8.0 ml.). The insoluble solid was collected and crystallised from acetic acid to give the corre-

sponding 2-*N*-oxides (IIIa), (IIIb), or (IIIe) (Table 2), ν_{\max} 3400, 3200—3100 (br.) (NH), and 1680 cm^{-1} .

(b) Alternatively the 3-aminobenzo-1,2,4-triazine derivatives (IIc) or (IIId) in glacial acetic acid were treated at room temperature for 80 hr. with 30% hydrogen peroxide as in (a) above, and the crude product crystallised from acetic acid–water to give the 2-*N*-oxides (IIIc) or (IIId) (Table 2), ν_{\max} 3400, 3200—3100 (br.) (NH), and 1680 cm^{-1} .

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Synthesis of 1-Hydroxyquinoxalin-2(1*H*)-one 4-*N*-Oxides

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Summary Benzofuroxan and its 5-substituted derivatives condense with benzoylacetonitrile in ethanolic ammonia to yield the corresponding 2-cyano-3-phenylquinoxaline 1,4-di-N-oxides which are smoothly converted in warm ethanolic sodium ethoxide into 1-hydroxyquinoxalin-2(1H)-one 4-N-oxides: the course of these reactions is discussed.

RECENTLY, two research groups^{1,2} have reported an elegant general route to quinoxaline 1,4-di-N-oxides involving the base-catalysed condensation of benzofuroxans with active methylene compounds. The mechanisms of these interesting reactions have not been elucidated, but it might be

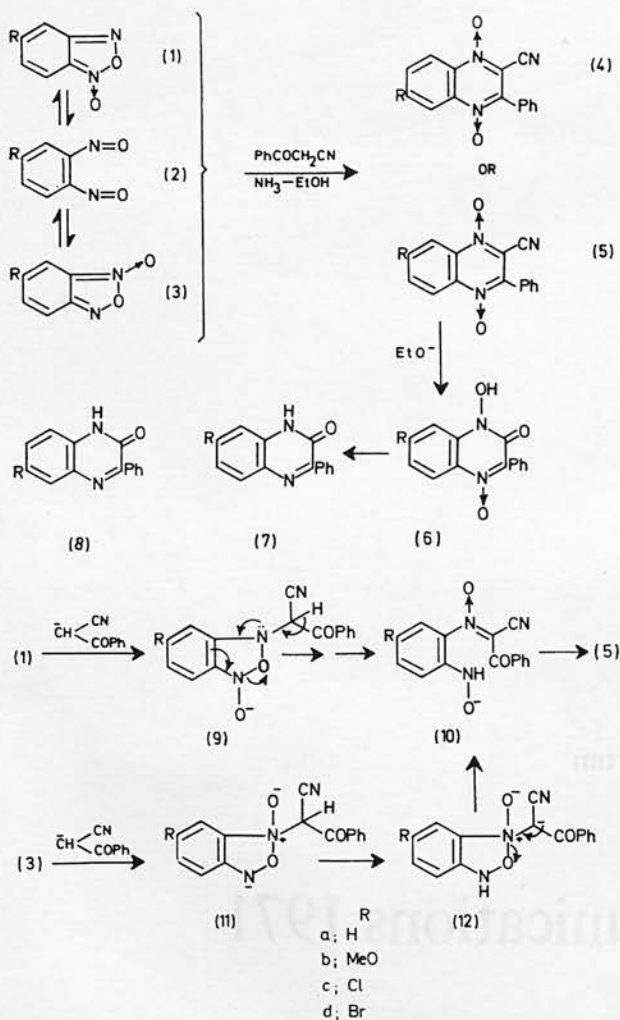
a synthetic route to 1-hydroxyquinoxalin-2(1H)-one 4-N-oxides (required in connection with other studies⁴) which provides some information on this point.

Benzofuroxan (**1a**) condensed readily with benzoylacetonitrile in ethanolic ammonia at room temperature to give the quinoxaline di-N-oxide (**5a**) (Table). In accord

Quinoxaline di-N-oxides and 1-hydroxyquinoxalin-2(1H)-one 4-N-oxides^a

	Yield(%)	M.p. (°)
(5a)	70	208
(5b)	74	223
(5c)	75	218
(5d)	59	216
(6a)	67	196
(6b)	76	243
(6c)	76	228
(6d)	81	231

^a Satisfactory analyses and spectral data were obtained for all new compounds.



expected that, because of their tautomeric structure,³ substituted benzofuroxans would afford an isomeric mixture of two quinoxaline di-N-oxides. We now describe

with the assigned structure, warm ethanolic sodium ethoxide converted this product, with loss of the cyano-group,⁵ into the cyclic hydroxamic acid (**6a**) (Table) which gave a deep red colour⁵ with iron(III) chloride in ethanol and was converted in warm acetic anhydride into an acetoxy-derivative (**6a**; OAc for OH) with a characteristic⁶ carbonyl i.r. band at 1800 cm⁻¹ (cyclic :N-OAc). The substituted benzofuroxans (**1b-d**) also condensed readily with benzoylacetonitrile in ethanolic ammonia, but contrary to expectations a single product was formed (Table) in each case. A careful examination of the ¹H n.m.r. spectra of the crude products failed to reveal the presence of isomerides. The substituted di-N-oxides so obtained are formulated (Table) as (**5b-d**) rather than (**4b-d**) on the basis of their conversion (warm ethanolic sodium ethoxide) into the corresponding cyclic hydroxamic acids (**6b-d**) (Table) dithionite reduction of which afforded the quinoxalones (**7b-d**). The latter products were non-identical with the quinoxalones (**8b-d**) of established orientation^{4,7} and showed ¹H n.m.r. absorption in accord with the assigned structures.

Ring-opening of adducts (**9**) formed by nucleophilic attack at N-3 in the benzofuroxans (**1**), and cyclisation of the resulting hydroxylamino-nitrone intermediates (**10**) is a possible course for formation of the di-N-oxides (**5**). This mechanism is in accord with reaction of a 5(6)-substituted benzofuroxan in the more stable⁸ tautomeric form (**1**). An alternative course [(**3**) \rightarrow (**11**) \rightarrow (**12**) \rightarrow (**10**)] initiated by nucleophilic attack at N-1 is also possible¹ but would require reaction of a 5(6)-substituted benzofuroxan in the less stable form (**3**). Preferential nucleophilic attack at the 3-nitroso-group in the dinitroso-tautomers (**2b-d**) would also account for the formation of the di-N-oxides (**5b-d**). However, it is unlikely that the implied deactivation of the 4-nitroso-group by the substituent would be sufficient—especially in the halogeno-tautomers (**2c-d**)—to account for the predominant attack at the 3-nitroso-group

demanded by the observed orientation (5c—d) in the products.

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